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Neuromodulatory effect of subthalamic nucleus stimulation on spontaneous language production in Parkinson's disease

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Voor Pascal, Eva & Senne

...I am happy to have you home!

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List of publications

This doctoral thesis is based on the articles published or submitted in the following international peer-reviewed journals:

- Batens, K., De Letter, M., Raedt, R., Duyck, W., Vanhoutte, S., Van Roost, D., & Santens, P. (2014). Lateralized effects of subthalamic nucleus stimulation on semantic and syntactic performance in spontaneous language production in people with Parkinson's disease. *Journal of Neurolinguistics, 32*, 31-41.

- Batens, K., De Letter, M., Raedt, R., Duyck, W., Vanhoutte, S., Van Roost, D., & Santens, P. (2015). Subthalamic nucleus stimulation and spontaneous language production in Parkinson's disease: A double laterality problem. *Brain and Language, 147*, 76-84.

- Van Lier, S.*, Batens, K.*, Van Roost, D., Santens, P., Van Herreweghe, M. & De Letter, M., (accepted). The influence of subthalamic nucleus stimulation on pragmatic language production in Parkinson's disease. *Acta Neurologica Belgica.*

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List of abbreviations

% correct sentences	Percentage of correct sentences
Ampl	Amplitude
ASTA	Analysis of Spontaneous Speech in Aphasia
BDI	Beck Depression Inventory
BG	Basal ganglia
Bilateral off	Bilateral subthalamic nucleus stimulation off
Bilateral on	Bilateral subthalamic nucleus stimulation on
Caudate	Caudate nucleus
COWA	Controlled Oral Word Association
Cx	Cortex
DA	Dopamine
DBS	Deep brain stimulation
DIA-S	Dutch Intelligibility Assessment at sentence level
Freq	Frequency
GABA	Gamma-aminobutyric acid
Glu	Glutamate
GPe	Globus pallidus pars externa
GPi	Globus pallidus pars interna
LEDD	Levodopa-equivalent daily dose
Left only	Left subthalamic nucleus stimulation
MLU	Mean length of utterance
MOCA	Montreal Cognitive Assessment
MRI	Magnetic resonance imaging
NPT	Nijmeegse Pragmatiektest
NSVO-Z	Nederlandstalig spraakverstaanbaarheidsonderzoek zinsniveau
PD	Parkinson's disease
PD-left	Patient with Parkinson disease with predominant left hemispheric dopamine depletion

PD-right	Patient with Parkinson disease with predominant right hemispheric dopamine depletion
RAVLT	Rey Auditory Verbal Learning Test
RAVLT-ltm	Rey Auditory Verbal Learning Test - long-term recall
RAVLT-stm	Rey Auditory Verbal Learning Test - short-term recall
RAVLT-total	Rey Auditory Verbal Learning Test - total trials
Right only	Right subthalamic nucleus stimulation
SCWT-color-Word	Stroop color word
SNc	Substantia nigra pars compacta
SNr	Substantia nigra pars reticulate
Stand. Dev	Standard deviation
Str	Striatum
STN	Subthalamic nucleus
TEED	Total electrical energy delivered
Th	Thalamus
TTR	Type token ratio
UPDRS	Unified Parkinson's Disease Rating Scale
VL	Ventrolateral nucleus
ZvP	Ziekte van Parkinson

Summary

Parkinson's disease (PD) is one of the most frequent neurodegenerative disorders, which is characterized by an asymmetric degeneration of dopaminergic neurons. Besides the well-known speech disturbances, there is growing evidence that PD patients exhibit difficulties on all aspects of language. The underlying cause of these language deficits still forms a matter of debate. Although the majority of authors states that domain-general problems in cognitive control cause language disturbances, some initial indications impose themselves to suggest that the basal ganglia influence language in a domain-specific manner. Given the lateralized representation of both language functions and PD, investigating the relationship between both would provide interesting information, but has scarcely been examined.
Subthalamic nucleus deep brain stimulation (STN DBS) has become an established therapeutic option for advanced PD with motor fluctuations that are refractory to pharmacological treatment. The effect of STN DBS on language processes shows inconsistent results. By further unraveling the factors that influence the linguistic outcome in STN DBS, useful clinical information could be obtained, resulting in improvement of both motor and non-motor symptoms.

The main objective of this doctoral thesis was to identify linguistic and pragmatic deficits in spontaneous language production in PD patients with STN DBS. The application of STN DBS offers the opportunity to evaluate the effect of STN DBS in a unilateral way. As a result, the effect of STN DBS on hemisphere specific language processes can be evaluated in combination with asymmetric dopamine depletion. As little is known about the long-term effects STN DBS exerts on spontaneous language production, seven PD patients were monitored multiple times from baseline until one year after STN DBS surgery. The effect of STN DBS seems to be influenced by multiple factors, such as the stimulation parameters, medication dosage, intelligibility, mood, and neuropsychological performances. The interaction of these variables with STN DBS was evaluated to examine their influence on language outcome.

Especially the morphosyntactic elements of spontaneous language production of PD seemed divergent from normative data. PD patients produced shorter sentences that were more often incorrect. Our results suggested that PD patients may develop compensatory strategies to circumvent these morphosyntactic difficulties (e.g. excessive production of copula and modal verbs) depending on the asymmetric dopamine depletion. The effect of STN-DBS on spontaneous language production was also rather inconsistent in our studies. A striking change after STN surgery was the immediate reduction in the number of nouns without any supplementary changes in the course of the year. Again, asymmetric dopamine depletion seemed to influence the linguistic and pragmatic outcome of STN DBS, mainly for PD patients with predominantly left hemispheric dopamine depletion. The spontaneous language production of these patients improved with bilateral STN stimulation. The longitudinal results indicated that this improvement with bilateral stimulation could not be retained at an individual level (with large inter- and intra-subject variability). Furthermore, these longitudinal results showed that levels of dopaminergic medication in combination with STN DBS partly determined the outcome in terms of spontaneous language production.

In conclusion, it can be stated that STN DBS in PD influences both linguistic and pragmatic elements of spontaneous language production. Further research is necessary to determine which other variables, beside asymmetric dopamine depletion and levels of dopaminergic medication, contribute to the outcome of STN DBS on spontaneous language production.

Samenvatting

De ziekte van Parkinson (ZvP) is één van de meest voorkomende neurodegeneratieve ziektes, gekenmerkt door een asymmetrisch verlies van dopaminerge neuronen. Er zijn toenemende aanwijzingen dat mensen met de ZvP, naast duidelijk omschreven spraakstoornissen, ook problemen ervaren op alle verschillende taaldomeinen. De onderliggende oorzaak van deze taalproblemen blijft tot op heden een punt van discussie. Al suggereert het merendeel van de onderzoekers dat de taalstoornissen voortvloeien uit algemene problemen op het gebied van cognitieve controle, toch zijn er ook aanwijzingen dat de basale ganglia op een domeinspecifieke manier de taal beïnvloeden. Aangezien zowel taalprocessen als de ZvP een gelateraliseerde representatie kennen, is het interessant om de interactie tussen beide te onderzoeken, hetgeen tot op heden maar zelden is gebeurd.

Diepe hersenstimulatie van de subthalamische kern (STN DBS) is uitgegroeid tot een gevestigde therapeutische optie bij mensen met de ZvP in een gevorderd stadium, waarbij de motorische fluctuaties met medicatie niet meer kunnen behandeld worden. De resultaten van STN DBS op taal zijn zeer uiteenlopend. Door te ontrafelen welke factoren het effect van STN DBS op taal beïnvloeden, wordt het wellicht mogelijk de klinische begeleiding te optimaliseren. Op die manier kunnen niet enkel de motorische symptomen, maar ook de niet motorische symptomen na STN DBS worden verbeterd.

De belangrijkste doelstelling van dit proefschrift bestond erin de linguïstische en pragmatische kenmerken van de spontane taalproductie te identificeren bij mensen met de ZvP die STN DBS hebben ondergaan. De elektroden die in beide subthalamische kernen zijn geplaatst, kunnen afzonderlijk geactiveerd worden. Dit biedt de mogelijkheid om na te gaan hoe unilaterale stimulatie gelateraliseerde taalprocessen beïnvloedt. Doordat de ZvP gekenmerkt wordt door een asymmetrisch dopamineverlies, beïnvloedt ook dit mogelijks de spontane taalproductie. Over de evolutie van de spontane taalproductie bij mensen met de ZvP is er nog maar weinig geweten. Daarom werden er zeven patiënten met de ZvP opgevolgd van voor hun ingreep tot één jaar erna. Voorafgaand wetenschappelijk onderzoek heeft aangetoond dat het effect van diepe

hersenstimulatie op niet-motorische symptomen beïnvloed wordt door meerdere factoren, zoals de stimulatieparameters, de dosering van de medicatie, de spraakverstaanbaarheid, de stemming en het neuropsychologisch functioneren. De invloed van deze variabelen op de spontane taalproductie bij STN DBS werd geëvalueerd.

Voornamelijk de morfosyntactische elementen van de spontane taalproductie bij mensen met de ZvP lijken af te wijken van de normatieve data. Mensen met de ZvP vormen kortere en minder correcte zinnen. Onze resultaten suggereren dat mensen met de ZvP mogelijks compensatiestrategieën (vb. overmatig gebruik van koppel- en modaal werkwoorden) gebruiken. Deze compensatiestrategieën zijn afhankelijk van het asymmetrisch dopamineverlies. Het effect van STN DBS op de spontane taalproductie, is net zoals in voorafgaande studies, sterk inconsistent. Een opvallende verandering bij mensen die net de diepe hersenstimulatie ingreep hadden ondergaan, was het verminderd produceren van zelfstandige naamwoorden. Opnieuw werd duidelijk dat asymmetrisch dopamineverlies de linguïstische en pragmatische elementen van spontane taal tijdens STN DBS lijkt te beïnvloeden. Het zijn voornamelijk mensen met een predominant dopamineverlies in de linker hemisfeer waarbij bilaterale stimulatie van de subthalamische kernen de correctheid van de spontane taalproductie positief lijkt te beïnvloeden. Uit de longitudinale resultaten blijkt nochtans dat dit niet te weerhouden valt op een individueel niveau en dat hier de grote zowel inter- als intra-subject variabiliteit werd benadrukt. Verder valt op dat, naast het asymmetrisch dopamineverlies, de verhouding tussen STN DBS en de dosis dopaminerge medicatie de spontane taalproductie beïnvloedt.

Tot besluit kan er gesteld worden dat STN DBS zowel de linguïstische als pragmatische elementen van spontane taalproductie bij de ZvP beïnvloedt. Verder onderzoek is noodzakelijk om bijkomende variabelen te belichten die naast asymmetrisch dopamineverlies en dopaminerge medicatie het effect van STN DBS op spontane taalproductie beïnvloeden.

General introduction & Research aims

PART 1

Parkinson's disease

Parkinson's disease (PD) is one of the most frequent neurodegenerative disorders characterized by progressive degeneration of the dopaminergic producing cells in the substantia nigra pars compacta, leading to dopamine deficits in the striatum and subsequent dysfunctions in the cortico-basal ganglia-thalamocortical circuits (Niethammer, Feigin, & Eidelberg, 2012). Besides the damage in the nigrostriatal system, PD is always accompanied by extensive extranigral pathology (Braak et al., 2003). This extranigral pathology is mainly caused by aggregates of a misfolded protein, α-synuclein (Spillantini et al., 1997), which gradually appears as Lewy neurites and Lewy bodies in selected nerve cells of both the central and enteric nervous systems. The widespread synuclein pathology causes multifocal neurodegenerative lesions that affect the central, peripheral, and autonomic nervous systems and many other organs (e.g. adrenals, retina, heart, skin) (Djaldetti, Lev, & Melamed, 2009; Wakabayashi, Mori, Tanji, Orimo, & Takahashi, 2010).

PD is generally described as a neurodegenerative disease that mainly causes motor symptoms. The four cardinal motor symptoms of PD are resting tremor, rigidity, akinesia or bradykinesia, and postural instability (Jankovic, 2008). The degeneration of the dopaminergic system progresses many years before classical motor signs arise (Nandhagopal et al., 2009). Motor symptoms of PD occur when striatal dopamine is depleted beneath a critical threshold of 60-80% (Fearnley & Lees, 1991; Lee et al., 2000). These motor symptoms do not only lead to gait problems, PD patients also exhibit problems with speech, writing, and swallowing. Beside the well-described motor signs, a large range of non-motor symptoms is commonly present in PD. The non-motor symptoms do not only occur in the advanced stages of the disease, but also in the early stages and they sometimes even precede the motor symptoms (Chaudhuri & Schapira, 2009). They comprise neuropsychiatric disturbances (e.g. depression, hallucinations, and anxiety), cognitive disturbances (e.g. executive dysfunction, attention deficits, and dementia), linguistic disturbances (e.g. semantic deficits, morphosyntactic deficits, and pragmatic deficits), sleep disorders (e.g. vivid dreaming, insomnia, and disturbances in REM-sleep), autonomic disturbances (e.g. constipation, orthostatic hypotension, and sweating), and sensory disturbances (e.g. impaired visual sensitivity, pain, and olfactory disturbances).

The majority of speech-language research within PD still mainly addresses the speech disturbances. Although publications on language problems in PD are increasing in number, their translation to the clinical field is limited. Prior to describing the language problems associated with PD in more detail in the next chapter, some anatomical and functional background information on the basal ganglia (BG) and its connections will be given.

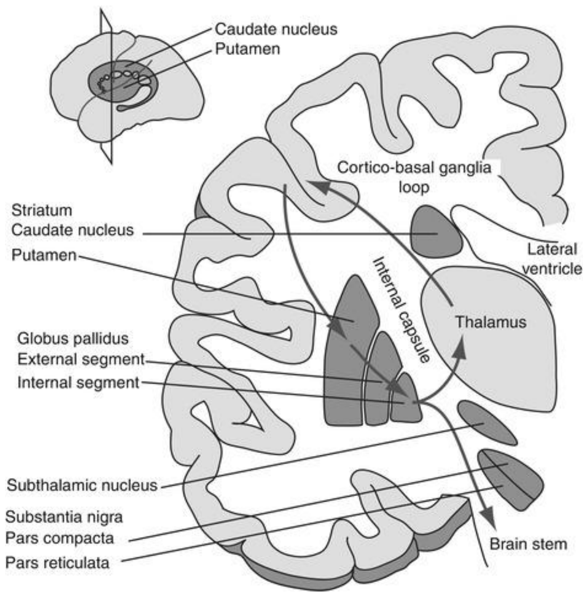

Figure 1.1 Coronal section of the brain showing the nuclei that form the basal ganglia. Figure reprinted from Nambu (2015) with permission (p 2).

The basal ganglia and its cortico-basal ganglia-thalamocortical loops

To understand the symptomatology of PD, some background information on the basal ganglia is necessary. The BG are a collection of bilaterally represented grey matter nuclei positioned deep within the white matter of the brain that are anatomically, neurochemically and functionally linked (Mink, 1996). The BG include the striatum (caudate nucleus and putamen), globus pallidus (globus pallidus internus, globus pallidus externus, and ventral pallidum), substantia nigra (pars compacta and pars reticularis), and subthalamic nucleus (STN) (Figure 1.1).

The BG are integrally involved in modulating sensorimotor, limbic, and cognitive information by connecting cortical and subcortical areas via complex neural circuits (Middleton & Strick, 2000). The cortico-basal ganglia-thalamocortical circuits seem to enable the BG to play a critical role in motor and cognitive control functions: (1) they are involved in learning activities that yield a reward, (2) they play a part in sequencing the individual elements that constitute a motor or cognitive "pattern generator", (3) and they interrupt an ongoing sequence, depending on external events and prior knowledge (Lieberman, 2002).

The basis of our knowledge of the anatomical and functional organization of cortico-basal ganglia-thalamocortical circuits is based largely on the work of Alexander & Crutcher (1990). They identified five parallel yet functionally segregated BG circuits based on their corticofrontal origin (a motor loop, an oculomotor loop, two prefrontal associative loops and an orbitofrontal limbic loop) (Figure 1.2).

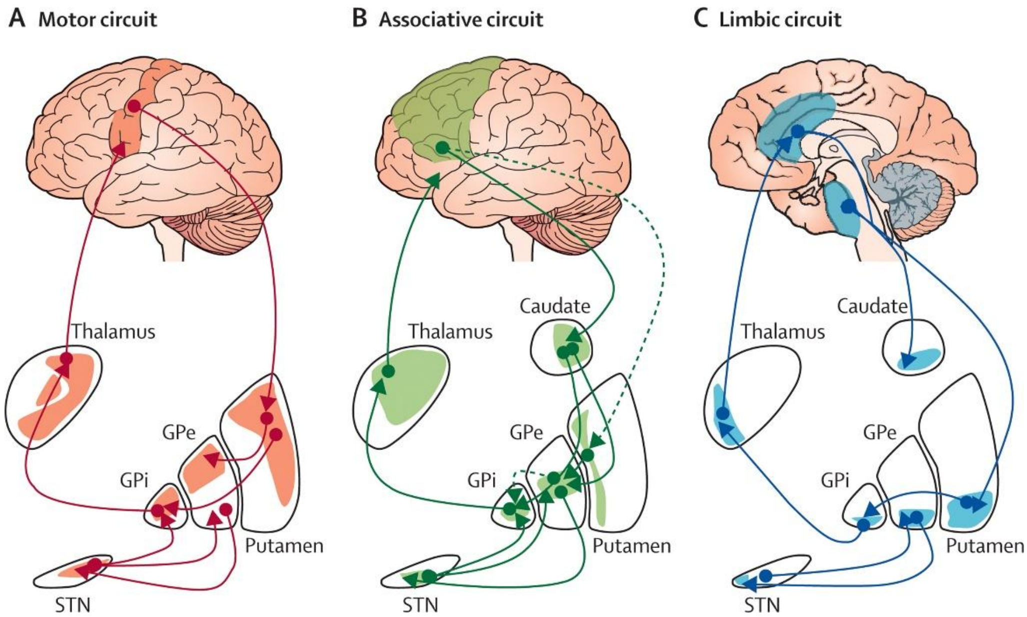

Figure 1.2 The functional organisation of the basal ganglia. The basal ganglia are divided into motor (A), two prefrontal associative (B), and orbitofrontal limbic (C) subregions, which are largely topographically segregated, as highlighted by areas coloured in red (motor cortex), green (prefrontal cortex), and blue (anterior cingulate cortex). Caudate = Caudate nucleus; GPe=globus pallidus externus; GPi=globus pallidus internus; STN=subthalamic nucleus. The oculomotor loop is not illustrated in this figure. Figure reprinted with permission from Rodriguez-Oroz et al. (2009).

The fibres within these cortico-basal ganglia-thalamocortical loops proceed for every nucleus of the BG in a somatotopically organized way (Romanelli, Esposito, Schaal, & Heit, 2005). Despite this high degree of neuronal specificity within the BG structures, there are indications of partial overlap and interactions between the circuits (Draganski et al., 2008; Haber & Calzavara, 2009; Romanelli et al., 2005). This convergence may play an important role in integrating information about different functional aspects of motor or cognitive domains in order to elicit the contextually most appropriate behavioural response (Draganski et al., 2008). Each of these large circuits can be divided into sub-circuits centred on sub-regions of the frontal cortical area with more specific functions. For example, in a recent diffusion-tensor MRI tractography study the authors were able to visualize two cortico-basal ganglia-thalamocortical loops projecting from the two sub-regions of Broca's area, pars triangularis (BA45) and pars opercularis (BA44), to an overlapping part of the anterior putamen (Ford et al., 2013).

Each BG circuit, whether it is a motor or a non-motor circuit, has an analogous loop-like configuration that contains at least three separate pathways: a direct, an indirect, and a hyperdirect pathway (DeLong & Wichmann, 2007) (Figure 1.3). The 'direct pathway' forms a loop from the frontal cortex connecting excitatory glutamatergic fibres to the striatum that in turn projects inhibitory γ-aminobutyric acid [GABA]ergic fibres directly to the internal segment of the globus pallidus (GPi) and substantia nigra pars reticulata (SNr). Subsequently, the GPi and SNr project inhibitory GABAergic fibres to various thalamic nuclei and these thalamic nuclei project back to the same cortical area from which the loop originated. The 'indirect pathway' originates from the same cortical areas as the 'direct pathway' and projects excitatory glutamaterigic fibres to the striatum. In turn, the striatum projects inhibitory GABAergic fibres to the external globus pallidus, which has inhibitory GABAergic projections to the subthalamic nucleus (STN). The STN sends excitatory glutamatergic fibres to the GPi/SNr, which sends GABAergic fibres to the thalamic nucleus. The thalamus sends glutamatergic fibres to cortical areas from where the loop started. Therefore, the opposing effects of the direct and indirect pathways influence the output activities of GPi/SNr. Applying this to motor activity, the direct pathway will facilitate movement, while the indirect pathway will suppress movement. The dopamine of substantia nigra pars compacta modulates the corticostriatal input by applying a dual effect on striatal neurons: exciting D1-receptor neurons in the direct pathway, and inhibiting D2-receptor-neurons in the indirect pathway (Obeso, Rodriguez-Oroz, Rodriguez, DeLong, & Olanow, 2000). The last discovered pathway is the hyperdirect pathway (Nambu, Tokuno, & Takada, 2002), which connects wide spread areas of the frontal lobe through excitatory glutamatergic fibres directly to the STN. In turn, the STN projects glutamatergic fibres to the GPI. As for both other pathways, the GPi sends GABAergic fibres to the thalamus, which sendglutamatergic fibres to the cortex.

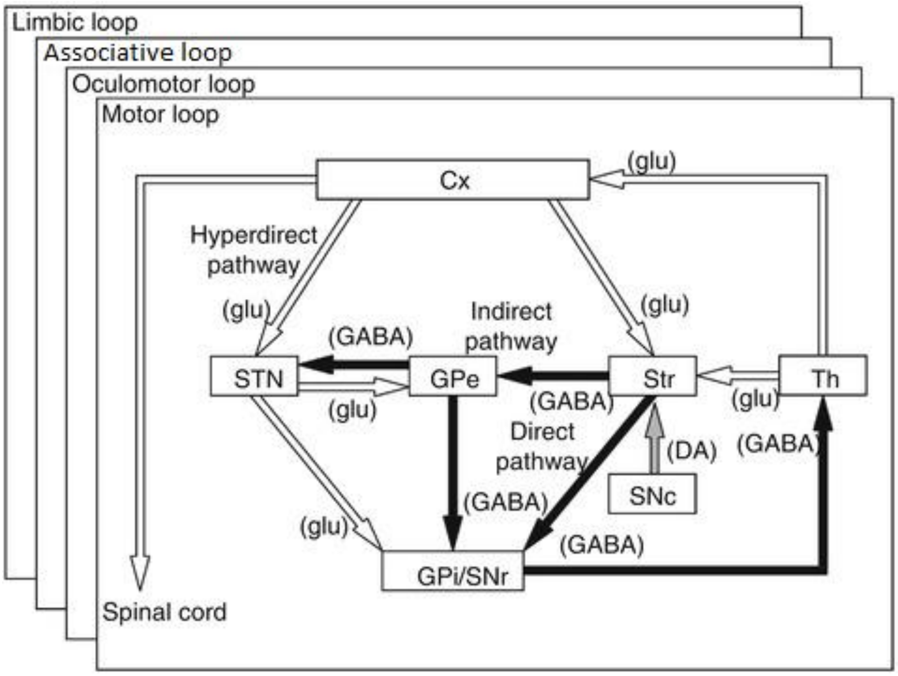

Figure 1.3 The classic pathophysiological model of the basal ganglia. Cx= cerebral cortex; Str= striatum; DA= dopamine; GABA= γ-aminobutyric acid; glu= glutamate; GPe= globus pallidus pars externa; GPi= globus pallidus pars interna; SNc= substantia nigra pars compacta; SNr= substantia nigra pars reticulate; STN= subthalamic nucleus; Th= thalamus. White arrows indicate excitatory projections; black arrows indicate inhibitory projections. Figure reprinted with permission from Nambu (2015).

Besides the involvement of the BG in the closed fronto-subcortical circuits, the BG structures also receive projections from non-circuit cortical areas, thalamic nuclei, cerebellum and the amygdalar nuclei, and also project to regions outside the five fronto-subcortical circuits, including inferotemporal, and posterior parietal cortex (DeLong & Wichmann, 2010; Middleton & Strick, 2000, 2002). Finally, the cortico-basal ganglia-thalamocortical circuits are mostly represented as a unilateral system, although interhemispheric connections also exist, but their influence on the cortico-basal ganglia-thalamocortical circuits have not been extensively explored (Lieu & Subramanian, 2012).

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Parkinson’s disease and language processes

The bulk of scientific language research in general and PD in particular, is conducted on the level of words and sentences, while the vast majority of verbal interactions in real life take place at discourse level (AbdulSabur et al., 2014). Language research at discourse level is methodologically more challenging due to the important interaction of cognitive, social, and linguistic features. However, spontaneous language analysis can offer a lot of useful information from multiple points of view. From a theoretical point of view, spontaneous language production makes it possible to examine the interaction between the various linguistic levels (e.g. phonology, semantics, morphosyntactics) by means of quantifying linguistic parameters (Prins & Bastiaanse, 2004). From a communicative point of view, it offers insight into how people use language in daily life. The use of language within the social and situational contexts of language can be defined as pragmatics. Both the theoretical and the communicative point of view have been used in this doctoral thesis to examine spontaneous language production in PD patients. Before the linguistic and pragmatic functions of spontaneous language production in PD are discussed in more detail, an overview is given on the organisation of language and the involvement of subcortical structures.

Hemispheric language organization and the involvement of subcortical structures

The cortical representations of phonological and syntactic language functions are lateralized strongly to the left hemisphere. Semantic functions on the other hand, exhibit a more bilateral representation (Dominey & Inui, 2009; Lindell, 2006; Menenti, Segaert, & Hagoort, 2012). The right hemisphere is suggested to support the more coarse-grained semantic processes while the left hemisphere conducts a more fine-grained processing (Jung-Beeman, 2005). One of the sparse studies on language lateralisation at discourse level found a clear distinction in semantic lateralisation between narrative production and comprehension (AbdulSabur et al., 2014). Narrative comprehension relied more on bilateral semantic processes, while narrative production remained predominantly lateralized to the left hemisphere. The outcome difference between narrative comprehension and production in this study was hypothesized to be due to the prior knowledge of the semantic relationship between the different elements of the unfolding story. When somebody tells a story himself, that person is aware of the semantic relationships between the different elements in the story before he speaks, while the listener has to comprehend the underlying semantic relationships of elements in real time, which is assumedly more demanding (AbdulSabur et al., 2014).

The right hemisphere has been proposed to be crucial in mediating prosodic and paralinguistic aspects of language (although not further specified) in both production and comprehension (Lindell, 2006). In line with the prosodic and paralinguistic processing, the right hemisphere plays a vital role in the pragmatic functions of language necessary to interpret utterances in their context (Lindell, 2006; Vigneau et al., 2011). In order to produce and interpret discourse, people need to be able to glue all pieces together and make a cohesive and coherent story, in which the whole is more than the sum of its elements (Gernsbacher & Kaschak, 2003).

Since the end of the 19th century, researchers have been speculating about the involvement of the BG in language processes (Broadbent, 1872; Marie, 1906; Wernicke, 1874). The introduction of pallidotomy in the treatment of Parkinson disease led to a regained interest in the nineteen seventies, with reports of linguistic disturbance caused by the ablation or intra-operative stimulation of the dominant globus pallidus (Svennilson, Torvik, Lowe, & Leksell, 1960; Van Buren, Li, & Ojemann, 1966). In the late twentieth century, the interest peaked again with the development of imaging techniques that left no doubt that BG infarcts and haemorrhages in the dominant hemisphere could impair language or mimic aphasias (Carrera & Bogousslavsky, 2006; Klostermann, Krugel, & Wahl, 2012; Nadeau & Crosson, 1997; Wallesch, 1997). However, the variabilities in the type and severity of aphasia were striking and little or no correlation between localization and type of aphasia could be made (Weiller et al., 1993). These findings led to one of the early hypotheses that the observed language deficits were not the result of a lesion in the BG as such but of cortical hypoperfusion (diaschisis) caused by a lesion in the BG (Nadeau & Crosson, 1997). A study using perfusion and diffusion-weighted magnetic resonance imaging confirmed this hypothesis, as aphasia only occurred when hypoperfusion in the language-eloquent cortical areas were detectable (Hillis et al., 2001). Because this hypothesis was based on studies examining language deficits following vascular lesions, Copland (2003) compared the results of patients with vascular lesions and PD patients in a semantic priming task. The patients with PD exhibited similar language deficits as patients with neurovascular lesions, which made the hypothesis of hypoperfusion questionable, as one would not expect the same extent of cortical hypoperfusion in PD as in vascular problems (Copland, 2003).

Research on language deficits in PD has allowed to suggest that PD can compromise all aspects of language comprehension and production including morphosyntax (Colman et al., 2009; Longworth, Keenan, Barker, Marslen-Wilson, & Tyler, 2005; Ullman, 2004; Ullman et al., 1997), lexical-semantic (Angwin et al., 2009; Castner et al., 2007; Crescentini, Mondolo, Biasutti, & Shallice, 2008), and high-level language abilities (Illes, 1989; Illes, Metter, Hanson, & Iritani, 1988; McNamara & Durso, 2003; Murray, 2000; Murray & Lenz, 2001; Pignatti, Ceriani, Bertella, Mori, & Semenza, 2006; Zanini, Tavano, & Fabbro, 2010). The language-related functions that are allocated to the striatum and their associated neural networks of the cortico-basal ganglia-thalamocortical loops (DeLong & Wichmann, 2007; Middleton & Strick, 2000a, 2000b), especially the fronto-striatal circuit, are diverse.

In terms of morphosyntax, PD patients have been reported to have problems with sentence comprehension, especially when sentences are ambiguous (Grossman, Carvell, Stern, Gollomp, & Hurtig, 1992; Grossman et al., 2002). Initially, Grossman et al. (1992) suggested that these deficits were linked to attention deficits, but in more recent work they attributed the grammatical deficits to slowed lexical access (Grossman et al., 2002). Neurophysiological research indicated that the BG do not play a role in the early automatic rule based syntactic processing but in the late controlled syntactic processing (Friederici, Kotz, Werheid, Hein, & von Cramon, 2003; Kotz, Schwartze, & Schmidt-Kassow, 2009). This dissociation between the initial automatic and later controlled processes in PD patients was not only found in syntactic processes but also in semantic and morphological processes. This allowed to assume that BG deficits in PD caused a domain-general problem. Longworth et al. (2005) suggested that the late controlled processes required inhibition of competing alternatives. For example, to be able to produce a correctly inflected verb in a sentence, it requires a correct selection of morphological features. In language, the enhancement of desired elements and the inhibition of unwanted elements, which is necessary to generate an intended sequence, is present at almost every linguistic level. Some researchers claimed it was not the inhibition itself, but the deficits in synchronising the sequence that caused the late linguistic processing problems (Kotz et al., 2009).

An alternative hypothesis for the morphosyntactic problems in PD was the declarative/procedural model of Ullman and colleagues (1997). They proposed that PD patients had problems generating rules, due to an impaired procedural memory system. The procedural memory system is one of the two systems of the declarative/procedural model. The declarative memory system contains the mental lexicon, and is embedded in the temporal cortex. The fronto-striatal network constitutes the procedural system that regulates grammatical rules (Ullman et al., 1997).

For semantic functions, it was especially the processing of verbs that seemed to be dysfunctional (Boulenger et al., 2008; Cotelli et al., 2007; Peran et al., 2003). The distinction between noun and verb processing showed that the frontal cortical motor areas have a contribution in verb processing (Boulenger et al., 2008). Others suggested that the BG seemed to be involved in monitoring the selection of lexical items by suppressing less adequate lexical alternatives (Copland, 2003; Crescentini et al., 2008; Crosson, 1985; Wallesch, 1997). Comparable to the morphosyntactic hypothesis, the BG would inhibit less adequate lexical alternatives under semantic and contextual constraints and only passed the most suited information on to the thalamus, in turn giving the ‘central commands’ for fronto-cortical ‘word release’ (Wallesch, 1997). Also for the deficits in verb generation in PD, an underlying general executive dysfunction has been proposed (Cotelli et al., 2007).

The question governing the literature is the question if language deficits in PD are primary or rather secondary to various cognitive dysfunctions. The ascribed cognitive functions can be classified to a large extent to executive dysfunctions (executive functions cover sustained attention, initiation/inhibition, flexibility to shift, planning, working memory and response selection), which in turn can be traced back to deficits in cognitive control (Niendam et al., 2012). Therefore, the dominant view to date is that language deficits are caused by a domain-general problem in cognitive control. Even though the domain-general contribution of the BG in cognitive functioning is generally accepted, some have postulated that BG might subserve some language-specific function. By means of an fMRI study Chan, Ryan, and Bever (2013) tried to unravel whether the role of the BG in sequencing was the same for every task or if the BG played a language specific sequencing role. The results suggested that the BG modulated linguistic sequencing in a domain-specific manner. This hypothesis got support by a diffusion MRI study visualizing, for the first time, segregated loops from Broca's area to the BG (Ford et al., 2013).

As for the cortical lateralisation of language function, there seems to be a similar lateralisation for subcortical language functions that parallels the cortical language predominance (Dominey & Inui, 2009; Friederici, 2011; Ullman, 2004). One study suggested that the non-dominant BG are also active during language processes, but rather as a suppressor of interference in language processing by non-dominant frontal structures (Crosson et al., 2003).

Spontaneous language production in PD

The scientific research on language in PD mainly focused on words and sentences level, while studies on spontaneous language production are scarce. Illes et al. (1988) were among the first to examine spontaneous language production in PD. They reported that PD patients used simplified sentence structures with more silent hesitations and pauses at critical sites in the sentences and considered these changes in spontaneous language production to be an adaptation to their motor speech difficulties (Illes et al., 1988). On the other hand, in a companion study they concluded that PD patients' sentence structure seemed syntactically intact compared to other neurodegenerative disease like Alzheimer's disease and Huntington's disease (Illes, 1989). The correlation between grammatical changes and motor speech performances remained the prevailing assumption, although the emphasis shifted to cognitive abilities (Murray, 2000; Murray & Lenz, 2001). PD patients who had a better short-term memory and attention span produced longer syntactically complex utterances. Concerning the spontaneous production of nouns and verbs, no difference between PD patients and healthy controls could be found, while in the picture naming task PD patient produced significantly less verbs than healthy controls. This result suggested that the use of verbs under specific task constraints could cause impairments, more than verb retrieval deficits itself (Pignatti et al., 2006). The influence of implicit and explicit memory subsystems was examined by analysing the spontaneous language production of bilingual PD patients (Zanini et al., 2010). All included PD patients acquired their second language formally at school by the age of six. Hereby, the authors claimed that the native language requested largely implicit memory functions while the second language relied more on explicit memory functions. PD patients exhibited more phonological, morphological, and syntactical errors in their native language than in their second language. These findings suggested that PD patients exhibited more implicit than explicit language processing impairments.

Pragmatic language functions in PD

Next to the theoretical information, provided by the analysis of linguistic parameters, investigation of the spontaneous language production on a pragmatic level, offers interesting information on the daily use of language. Pragmatics refers to the ability to use and interpret verbal and nonverbal language appropriately within a social context and requires a degree of inference and interpretation (Perkins, 2012). Hereby, pragmatics relies not only upon an intact language system, but also requires knowledge of the specific social context, its interlocutors, and a general knowledge of the world (Martin & McDonald, 2003). As Martin and McDonald (2003) stated “It relies upon ‘higher order’ abilities whereby numerous cognitive systems interact in order that knowledge of context and language can combine to generate novel inference specific to each communicative act”. Due to high interplay of cognitive, social, and linguistic functions and its strong relationship with frontal areas, one can expect that PD patients exhibit certain pragmatic deficits (Holtgraves, McNamara, Cappaert, & Durso, 2010). In terms of pragmatic comprehension PD patients are poorer in the interpretation of figurative language (Lewis, Lapointe, Murdoch, & Chenery, 1998; Monetta, Grindrod, & Pell, 2009; Monetta & Pell, 2007), irony (Monetta et al., 2009), inference, humour (Berg, Björnram, Hartelius, Laakso, & Johnels, 2003), and speech acts (the specific intention a person anticipates to convey with an utterance) (Holtgraves et al., 2010; McNamara & Durso, 2003). With respect to pragmatic production, PD patients are impaired in stylistics, gestures, prosodics (McNamara & Durso, 2003), and turn taking (Griffiths, Barnes, Britten, & Wilkinson, 2011). In conversations, their utterances are less informative, show more or less explicit symptoms of word search and they might use more atypical wording (Holtgraves, Fogle, & Marsh, 2013; Saldert, Ferm, & Bloch, 2014). While the gestural, facial, and prosodic impairments are influenced undoubtedly by motor deficits, cognitive dysfunctions were suggested to underlie the other pragmatic function impairments (McNamara & Durso, 2003). For example, executive functions seems to be correlated with speech act comprehension (Holtgraves et al., 2013; Holtgraves et al., 2010), whereas comprehension of metaphor is correlated with working memory (Monetta et al., 2009; Monetta & Pell, 2007).

Even a small deterioration in one of the listed pragmatic functions might lead to a decreased quality of communication, increasing isolation, and a potential reduction of the quality of life (Miller, Noble, Jones, & Burn, 2006). Unfortunately, PD patients do not seem to be aware of their pragmatic shortcomings in contrast to their spouses and caregivers (McKinlay, Dalrymple-Alford, Grace, & Roger, 2009).

Asymmetric dopamine depletion in PD

A hallmark of PD is the asymmetry of motor symptoms, which reflects the asymmetric reduction of dopaminergic neurons (Djaldetti, Ziv, & Melamed, 2006; Kempster, Gibb, Stern, & Lees, 1989). This unilateral predominance of symptoms is generally noticeable throughout the course of the disease, even long after the disease becomes clinically bilateral (Antonini et al., 1995; Cronin-Golomb, 2010; Djaldetti et al., 2006). The brain tries to mitigate the dopamine deficiencies at different levels of the system. At synaptic level compensatory mechanisms such as increased dopamine synthesis and turnover, downregulation of the plasma membrane dopamine transporter and regulatory changes in dopamine receptors are described (Appel-Cresswell, de la Fuente-Fernandez, Galley, & McKeown, 2010). The compensatory neural responses that have been described at system level include a wider activation of cortical areas, an increased excitability of cortical areas, and the involvement of the contralateral hemisphere (Kojovic et al., 2012;

Spagnolo et al., 2013). This compensatory reorganization can influence the interhemispheric balance (Spagnolo et al., 2013). For example in motor tasks, the lateralized dopamine deficits are compensated by expanding the normal motor network to areas that are usually only activated in complex movements and/or by increasing the excitability of motor areas. In early PD, this increased excitability is only present in the most affected hemisphere, creating an imbalance between both hemispheres. As PD advances, this imbalance disappears, due to an increased excitability of both hemispheres (Spagnolo et al., 2013).

Although motor problems are the most visible lateralized symptoms, the asymmetric degeneration is also present in non-motor and cognitive functions (Cubo, Martinez Martín, Martin-Gonzalez, Rodríguez-Blázquez, & Kulisevsky, 2010; Kempster, Gibb, Stern, & Lees, 1989; Riederer & Sian-Hülsmann, 2012; Verreyt, Nys, Santens, & Vingerhoets, 2011). For example, difficulties with orientation, mental imagery, and visuospatial attention are observed in PD patients with more severe right-hemispheric dopamine depletion. On the other hand, problems in verbal memory are more associated with profound nigrostriatal degeneration in the left hemisphere. Some cognitive functions however, such as executive functions are less consistently lateralized (Verreyt et al., 2011).

Given the hemispheric specialisation of language functions, differential effects depending on the asymmetry of dopamine depletion can be expected. Despite the lateralized representation of language, the correlation of asymmetric degeneration of nigrostriatal networks and language has rarely been examined, merely as a part of general cognitive studies (Verreyt et al., 2011). The overall conclusion of these studies indicated that patients with more severe left-hemispheric dopamine depletion showed impairments in naming and verbal expression. Only one study specifically compared the spontaneous language production of PD patients depending on the asymmetric dopamine depletion. Patients with more severe right-hemispheric dopamine depletion were found to produce significantly fewer verbs and a more simplified linguistic output than patients with more severe left-hemispheric dopamine depletion. Because pragmatic processes are closely related and associated with dopaminergic networks of the right frontal lobe, Holtgraves et al. (2010) suggested that decreased linguistic complexity reflects a pragmatic deficit of the right frontal cortex. In addition, the dopamine sensitivity seems to be influenced by asymmetric dopamine depletion. After Levodopa intake, PD patients exhibited a larger dopamine-related effect on semantic processing in the less affected hemisphere (De Letter, Van Borsel, & Santens, 2009). Both studies emphasize the different involvement of both hemispheres, reflecting asymmetrical alterations in linguistic processing related to the asymmetric dopaminergic depletion.

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The effect of deep brain stimulation on language processes in Parkinson's disease

Deep brain stimulation (DBS) is a neurosurgical technique in which one or more electrodes are chronically implanted in a specific region of the brain (Okun, 2012). An impulse generator connected to the electrodes provides electrical pulses to the targeted brain tissue to modulate the neural signalling (Benabid, 2003). Each electrode has multiple contacts (number of contacts varies depending on the type of electrode) of which the best-positioned one(s) in the target area are activated. DBS has become an established therapeutic option for advanced PD with motor fluctuations that are refractory to medical treatment (Kleiner-Fisman et al., 2006; Klostermann, Krugel, & Wahl, 2012). DBS was introduced in the early nineties as a save alternative for lesional surgery of the thalamus or pallidum, because bilateral lesional surgery was associated with unacceptable speech, swallowing and cognitive deficits (Okun & Foote, 2010). The advantage of DBS is the reversibility and adjustability, whereby the parameters of the stimulation can be adapted (amplitude, pulse width and frequency) to the specific needs of the patient (Limousin et al., 1995). At first, the thalamus and the internal segment of the GPi were the stimulation targets of choice. Although stimulation of the thalamus results in a substantial tremor reduction, it has a poor effect on the other cardinal motor symptoms. The same accounts for the stimulation of the GPi, which had unsatisfactory results on akinesia (Lukins, Tisch, & Jonker, 2014). Nowadays, the subthalamic nucleus (STN) is considered generally the target of choice, although other targets, such as the pedunculopontine nucleus and zona incerta, have been recently explored.

The STN (former anatomical name: corpus Luysii) is a relatively small nucleus of the BG (160 mm^3 in humans) (Yelnik, 2002) and is located ventrally to the zona incerta and dorsally to the cerebral peduncle (Nambu, Tokuno, & Takada, 2002). As other nuclei of the BG, the STN can be subdivided into different parts, each with their own connections and functions (Figure 3.1). The large dorsolateral area of the STN, the sensorimotor part, receives predominant projections from the motor cortex in a somatotopically organized way. The ventral medial, the associative part, receives preferentially projections from the prefrontal cortex, whereas the medial tip of the STN, the limbic part, connects with the anterior cingulate cortex. In STN DBS for PD, the stimulating electrodes are aimed at the dorsolateral part of the STN. However, due to the small volume of the STN and the tight intermingling and interactions of the different subparts of the STN, diffusion of the electrical current to associative and limbic areas is common.

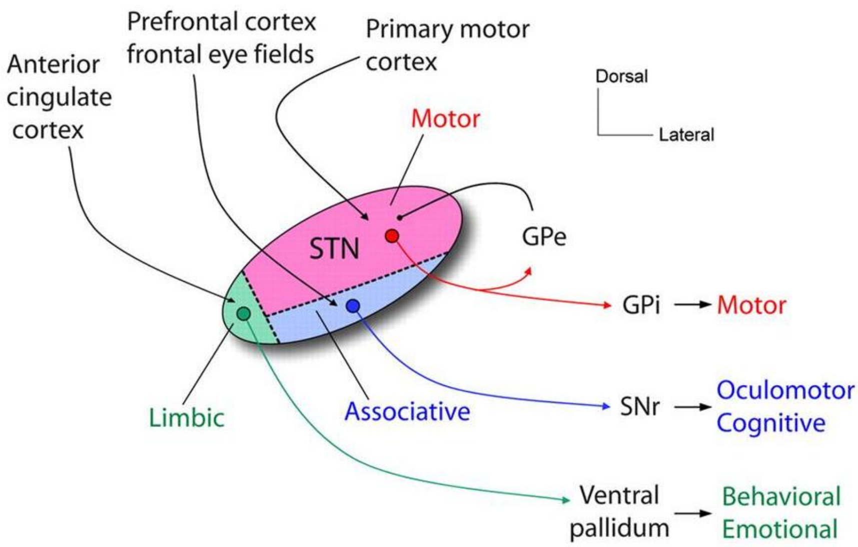

Figure 3.1 Schematic representation of the subthalamic nucleus. STN= subthalamic nucleus; GPe= globus pallidus externus; GPi= globus pallidus internus; SNr= substantia nigra pars reticularis. Figure reprinted with permission from Benarroch (2008) p1991-1995.

Although the exact mechanisms of DBS remain to be elucidated, the classic hypothesis is that STN DBS mimics an ablative lesion by suppressing output from the STN (Benabid, Chabardes, Mitrofanis, & Pollak, 2009). Different mechanisms can be involved separately or combined, to achieve this functional inhibition (Benabid et al., 2009): (1) jamming, altering the firing pattern so that abnormal oscillations desynchronize (2) extinction or strong inhibition of neuronal firing (neuronal silencing) (3) direct excitation of local inhibitory afferent neurons reducing the neuronal output. An alternative explanation for the efficacy of STN DBS is that stimulation results in a regular, high-frequency neuronal signal that does not necessarily restore to pre-pathological states, but to some third state regularizing neural firing patterns across the cortico-basal ganglia-thalamocortical network (Carlson, Cleary, Cetas, Heinricher, & Burchiel, 2010). The effect of STN stimulation clearly goes beyond local neuronal cell bodies and axon located around the electrical field and induces modifications within the entire cortico-basal ganglia-thalamocortical network (Thobois et al., 2007). This circumstance suggests that studies examining stimulation effects have to be interpreted in terms of functional connectivity between different brain areas.

High-frequency stimulation in the STN improves all cardinal motor symptoms of PD, allowing a strong reduction of dopaminergic drug treatment (Fasano, Daniele, & Albanese, 2012). This medication reduction subsequently leads to additional benefits, by decreasing or eliminating motor fluctuations, dyskinesia, and other complications of medication (Kleiner-Fisman et al., 2006). Not every PD patient benefits from STN DBS and an adequate patient selection is important. Patients clinically diagnosed with idiopathic PD, with an excellent Levodopa responsiveness, without severe cognitive deficits or dementia, are eligible candidates for STN DBS (Benabid et al., 2009). The global consensus is that surgery is proposed when motor complications cannot be adequately managed anymore by pharmacological means.

However, recent research has suggested to introduce STN DBS earlier in the course of the disease, when motor fluctuations are still relatively mild, as it results in a better outcome compared to best medical treatment for patients with PD (Schüpbach et al., 2007; Schüpbach et al., 2013; Schüpbach et al., 2014). Furthermore, earlier implanted PD patients preserve more autonomy compared to patients undergoing late STN DBS surgery (Merola et al., 2015).

The positive effect of STN DBS on motor symptoms has been demonstrated up to 10 years after surgery, except for speech, which generally deteriorates in response to STN DBS (Castrioto et al., 2011; Fasano et al., 2010; Krack et al., 2003; Tripoliti et al., 2011). However, after the fifth year of stimulation the beneficial effect of STN DBS on bradykinesia starts to reduce, postural instability starts to appear, and this usually in combination with a clear decrease in daily functioning (Fasano et al., 2010). Because STN DBS does not hold neuroprotective characteristics (Hilker et al., 2005), the disease progression together with the appearance of medication and stimulation resistant symptoms may be responsible for the partial reduced effect of STN DBS within the later course of the disease (Fasano et al., 2010).

In contrast to motor symptoms the effect of STN DBS on non-motor symptoms is highly variable. In a systematic review on the effect of STN DBS on behavioural symptoms, three important changes were identified (Temel et al., 2006): cognitive dysfunctions (41% of the patients), depression (8% of the patients), and (hypo)mania (4% of the patients). Remarkably, STN-DBS seems to evoke contradictory responses only for cognitive functions that demand a high degree of cognitive control (Campbell et al., 2008; Funkiewiez et al., 2004; Morrison et al., 2004; Temel et al., 2006; Witt et al., 2004). The most reported cognitive decline is the decrease in verbal fluency (verbal fluency is a cognitive function that facilitates information retrieval from memory; Daniele et al., 2003; Moretti et al., 2003; Pillon et al., 2000), executive functioning (Kleiner-Fisman et al., 2006; Saint-Cyr, Trépanier, Kumar, Lozano, & Lang, 2000), attention (Saint-Cyr et al., 2000), working memory (Hershey et al., 2004; Saint-Cyr et al., 2000), mental speed (Moretti et al., 2003), and response inhibition (Hershey et al., 2004; Witt et al., 2004).

Depression after STN DBS can be elicited by three factors: (1) the postoperative decrease of anti-Parkinson medication, which may have a psychotropic effect (2) the direct influence on related limbic structures and/or (3) the current spread to the neighbouring structures, like the substantia nigra (Visser-Vandewalle, Temel, Van der Linden, Ackermans, & Beuls, 2004).

One of the hypothesis for the differential effect on some non-motor symptoms is that the regularizing neural firing pattern produced by STN DBS may improve motor performance, while it might interfere with the phasic burst firing related to cognitive control processes (Campbell et al., 2008; Hershey et al., 2008). Stimulation variables, such as the precise location of the active electrode contact and the extent of the field of stimulation, may influence the outcome (Morrison et al., 2004; Temel et al., 2006). Each function within the STN, and thus each cortico-basal ganglia-thalamocortical loop projecting to the STN, has a certain threshold of modulation whereby each circuit can be separately modulated depending on the level of current amplitude (Lozano, Dostrovsky, Chen, & Ashby, 2002; Temel, Blokland, Steinbusch, & Visser-Vandewalle, 2005). Additionally there seems to be a frequency-dependent modulation as well. Whereas high-frequency stimulation (≥ 130Hz) improves motor symptoms, it decreases verbal fluency and, conversely, low frequency worsens motor symptoms but improves verbal fluency (Wojtecki et al., 2006). In addition, the interaction of asymmetric dopamine depletion with STN DBS can determine the outcome (Hershey et al., 2008). This latter will be discussed in more detail further on in this chapter.

Effect of STN DBS on language processes

Effect of STN DBS on language has been tested by comparing pre-operative and post-operative language functioning under optimal anti-Parkinson medication and stimulation conditions (Heo et al., 2008; Moretti et al., 2003; Whelan, Murdoch, Theodoros, Hall, & Silburn, 2003). An alternative way to study the effect of STN DBS has been to compare patients' performances ON and OFF STN DBS at one specific moment after surgery. On average this moment has been set at least four months after surgery to reassure stable stimulation parameters (Castner et al., 2008; Castner et al., 2007; Homer, Rubin, Horowitz, & Richter, 2012; Schulz et al., 2012; Silveri et al., 2012; Zanini et al., 2003; Zanini et al., 2009). Both types of studies have shown that semantic and morphosyntactic processes response inconsistently to STN DBS, ranging from general improvement (Zanini et al., 2003; Zanini et al., 2009), to opposite effects depending on the linguistic parameter (Castner et al., 2008; Castner et al., 2007), to general decline (Schulz et al., 2012). Heterogeneity is not only present comparing all studies but also among the subjects of one study (Whelan et al., 2003), highlighting the extreme heterogeneity within the Parkinson population.

The effect of STN DBS on spontaneous language has been scarcely tested. Zanini et al. (2003) suggested that STN DBS reduced morphosyntactic errors and increased the number of words, due to a re-establishing of the intrinsic functional equilibrium within the BG and the corticostriatal circuitries. They were also the first who examined the longitudinal effect of STN DBS on language processes. The described language progression after STN DBS was present from the first month after surgery and remained throughout the rest of the year. Spontaneous language production has also been used once to evaluate the effect of electrode position within the STN. PD patients in whom besides the dorsolateral part of the STN also the ventral medial part was being stimulated, showed a generally decline in morphosyntactic elements of spontaneous language production and the variability of words, compared to stimulation of only the dorsoventral part of the STN (Homer et al., 2012) (Figure 3.1).

For pragmatic functions, only recently, a first study examining the effects of STN DBS on pragmatic comprehension was published. No effects of STN DBS were found on the comprehension of metaphors (Tremblay et al., 2015). To our knowledge, no studies have addressed the effect of STN DBS on pragmatic language production.

Asymmetric effect of STN DBS on language processes

DBS offers the opportunity to assess the effects of unilateral stimulation of the BG structures, as both electrodes are separately configurable (Castner et al., 2007). Due to the asymmetric reduction of dopaminergic neurons, differential effects of STN DBS might be expected. For example, unilateral STN DBS seems to affect differentially working memory and motor function depending on asymmetric dopamine depletion (Hershey et al., 2008). Motor function improved more with STN DBS on the more dopamine-denervated side of the brain than with STN DBS on the less dopamine-denervated side of brain. In contrast, the reverse pattern is visible for working memory, where STN DBS on the more dopamine-denervated side of the brain impaired working memory, whereas STN DBS on the less dopamine-denervated side did not. The authors also suggest that unilateral and bilateral STN DBS can influence both motor and cognitive functions differentially.

The evaluation of unilateral stimulation effects on language can be particularly interesting because of the strongly lateralized cortical and subcortical representations of language (AbdulSabur et al., 2014; Dominey & Inui, 2009; Friederici, 2011; Lindell, 2006). To our knowledge, Schulz et al. (2012) were the first to examine language outcomes after unilateral STN stimulation. They assessed sentence comprehension and phonologic and semantic verbal fluency in four stimulation conditions. Bilateral stimulation deteriorated all linguistic measurements, when compared to no stimulation. Left unilateral stimulation resulted in linguistic outcomes that were inferior to those obtained by right STN stimulation. These results were related to lateralization of cognitive functions (verbal memory, lexical selection, switching and serial ordering) and to the fact that stimulation parameters are generally tuned to optimal motor responses, instead of cognitive and linguistic functioning.

The effect of pharmacological treatment on language processes in PD

Levodopa is a dopamine precursor that since its introduction almost 50 years ago is viewed as the gold standard for the symptomatic treatment of motor symptoms in PD (Salat & Tolosa, 2013). Long-term Levodopa use may eventually be limited by the development of various treatment-related complications, which include response fluctuations, dyskinesias, and psychiatric abnormalities (Nutt et al., 2001). The effect of Levodopa on cognitive functions is complex, describing adverse as well as beneficial effects (Cools, 2006; Tomer, Aharon-Peretz, & Tsitrinbaum, 2007). The spatio-temporal progression of dopamine depletion has been put forward as possible explanation for these contrasting effects. In the early stage of PD, dopamine depletion is more pronounced in the dorsal part of the striatum and progresses in the later stage to the ventral part of the striatum (Cools, 2006). Hereby, Levodopa might improve in the early stage of PD cognitive functions that are associated with the severely depleted dorsal striatum while at the same time impair by overdosing other cognitive functions associated with the relatively intact ventral striatum (Cools, 2006). Furthermore, the prefrontal cortex contains a large number of dopamine receptors, thus high levels of Levodopa necessary to compensate striatal dopamine deficiency might impair frontal functions by overdosing the prefrontal cortex. It seems that both excessive as well as insufficient levels of dopamine can cause impairments. Levodopa administration will have paradoxical cognitive consequences depending on the task that needs to be executed, the brain region that is implicated, and the baseline levels of dopamine in that brain region (Cools & D'Esposito, 2011). The few studies exploring the effect of Levodopa on language, examined lexico-semantic processing. They indicated that Levodopa could re-establish semantic activation (Angwin et al., 2009; Arnott et al., 2010; Boulenger et al., 2008; Herrera & Cuetos, 2012). Especially verbs would be susceptible for improvement, due to the involvement of the frontal motor areas involved in action naming (Boulenger et al., 2008; Herrera & Cuetos, 2012, 2013).

Something that needs to be kept in mind when studying the effect of STN DBS is that most patients are still on, though significantly reduced, anti-Parkinson medication. While the motor effects of Levodopa closely resemble those of STN-DBS, both treatments can have opposite effects on cognitive functions (Funkiewiez et al., 2006). For example, planning functions, which are associated with dorsolateral prefrontal cortex–dorsal striatal circuits, encounter only negative effects from STN DBS stimulation, while combining both treatments has equivalent positive mood-related effects. Therefore, the way both treatments bring modifications to the non-motor striatal pathway seem to be different, although the net result can be the same (Mondillon et al., 2012). Recently, Mondillon et al. (2012) examined the combined effect of STN DBS and Levodopa. The combination of both therapies might be more beneficial than each therapy separately, provided that the dopaminergic medication is correctly dosed so that it can partly neutralize the stimulation-induced inactivation of the prefrontal cortex (Mondillon et al., 2012).

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Research aims

The main objective of this doctoral thesis was to identify the linguistic and pragmatic features of spontaneous language production in PD patients with STN DBS and to investigate the effect that STN DBS has on these features. For this purpose, three transversal studies and one longitudinal study were included in this doctoral thesis (each represented in a separate chapter). As some patients were included in several studies, an overview is given in Figure 4.1 of the included patients of each study. The detailed aims of every chapter are further explained below.

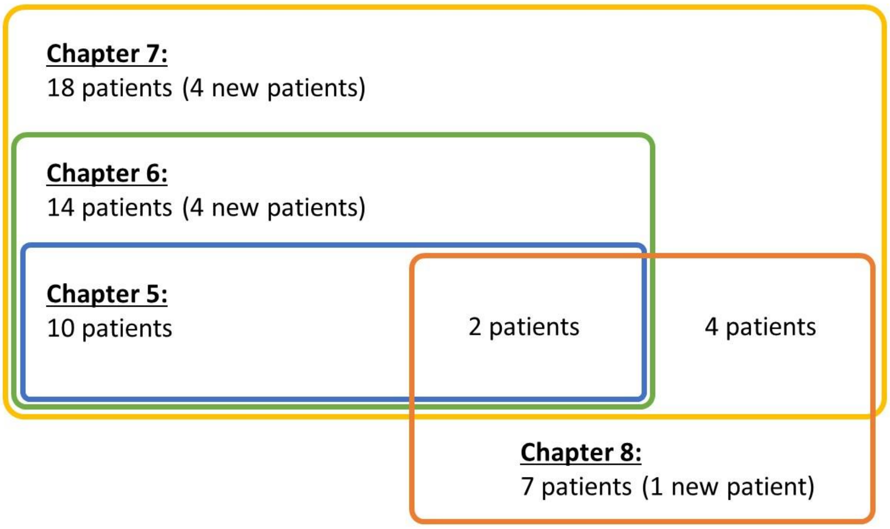

Figure 4.1 Overview on the number of patients included in one or more chapters.

A **first aim** was to investigate the spontaneous language production of PD patients and to compare the semantic and morphosyntactic characteristics of their spontaneous language with the present normative data. The effect of STN-DBS on spontaneous language production was explored in four stimulation conditions, so the net results of each electrode separately on spontaneous language production could be compared, next to bilateral stimulation on and off. These results are discussed in **Chapter 5**.

Hemispheric differences in both language processes and dopamine depletion in PD are two well-known phenomena. The **second aim** was to investigate whether asymmetric dopamine depletion influences the outcome of spontaneous language production in PD patients. To examine the interaction of STN stimulation with asymmetric dopamine depletion, the effect of each STN electrode separately on spontaneous language production was taken into account. These results are discussed in **Chapter 6**.

The **third aim** was to investigate the effect of STN-DBS on pragmatic production. All PD patients were examined in four stimulation conditions, so the net effect of each electrode separately on pragmatic production could be compared with bilateral stimulation on and off. Again asymmetric dopamine depletion was taken into account. These results are discussed in **Chapter 7**.

The **fourth aim** was to investigate the effect of STN-DBS on spontaneous language production within the first year after surgery and to compare these results with the spontaneous language production prior to surgery. Multiple variables have been suggested to influence the effect of STN stimulation. For the evaluation, seven variables were included: asymmetric dopamine depletion, lateralization of stimulation, stimulation parameters, medication dosage, speech intelligibility, mood, and neuropsychological performances. The relationship of these variables with the linguistic effect of STN-DBS were explored. These results are discussed in **Chapter 8**.

Publications

PART 2

Lateralized effects of subthalamic nucleus stimulation on semantic and syntactic performance in spontaneous language production in people with Parkinson’s disease

CHAPTER 5

Batens, K., De Letter, M., Raedt, R., Duyck, W., Vanhoutte, S., Van Roost, D., & Santens, P. (2014). Lateralized effects of subthalamic nucleus stimulation on semantic and syntactic performance in spontaneous language production in people with Parkinson’s disease. *Journal of Neurolinguistics*, 32, 31-41.

Abstract

Deep brain stimulation (DBS) of the subthalamic nucleus (STN) has become an established therapeutic option for advanced Parkinson's disease (PD). In this study, the lateralized effects of STN stimulation on spontaneous language production are explored, by comparing linguistic performance in different stimulation conditions with normative data of healthy subjects.

Language samples of ten PD patients with DBS of the STN were obtained in four stimulation conditions: bilateral stimulation on, bilateral stimulation off, stimulation of the left STN only and stimulation of the right STN only. The spontaneous language production differed from the normative data in all four stimulation condition. Especially morphosyntactic elements of spontaneous language production were altered. Despite these linguistic differences with normal controls, no significant differences between stimulation conditions were found. These results emphasize that the effect of STN stimulation on spontaneous language production is a complex interplay of multiple factors.

Highlights

- Semantic and syntactic features of spontaneous speech in PD are disrupted.
- Bilateral STN stimulation improves spontaneous language production.
- Stimulation of only the left STN affects linguistics parameters negatively.
- Multiple factors influence the effect of stimulation on spontaneous speech.

Keywords

Parkinson's disease, spontaneous language production, deep brain stimulation, lateralized effect

Introduction

There is increasing evidence that communication disorders in Parkinson's disease (PD) exceed motor speech disturbances and include impairments of language processing (Arnott et al., 2010; Castner et al., 2008; Copland, Sefe, Ashley, Hudson, & Chenery, 2009; Hines & Volpe, 1985; Illes, Metter, Hanson, & Iritani, 1988). Language alterations in PD affect all aspects of language comprehension and production, including morphosyntactic (Colman et al., 2009; Longworth, Keenan, Barker, Marslen-Wilson, & Tyler, 2005; Ullman et al., 1997), lexical-semantic (Angwin et al., 2009; Castner et al., 2007; Crescentini, Mondolo, Biasutti, & Shallice, 2008), and high-level language abilities (Illes, 1989; Illes et al., 1988; McNamara & Durso, 2003; Murray, 2000; Pignatti, Ceriani, Bertella, Mori, & Semenza, 2006; Zanini, Tavano, & Fabbro, 2010). Language dysfunctions are attributed to a disruption of normal functioning in the striatum and the associated neural networks of the cortico-basal ganglia-thalamocortical loops (DeLong & Wichmann, 2007; Middleton & Strick, 2000), as a consequence of neurodegeneration affecting mainly the dopaminergic midbrain nuclei. The majority of subcortical language models assign cognitive control functions to these cortico-basal ganglia-thalamocortical networks in a general way, such as the inhibition of competing alternatives and sequencing of processes (Chan, Ryan, & Bever, 2013), although there are some studies suggesting that the basal ganglia serve a language specific function (Chan et al., 2013; Robles, Gatignol, Capelle, Mitchell, & Duffau, 2005).

Deep Brain Stimulation (DBS) has become an established therapeutic option for advanced PD with motor fluctuations that are refractory to medical treatment (Kleiner-Fisman et al., 2006; Klostermann, Krugel, & Wahl, 2012). At present, in most centres performing DBS, the subthalamic nucleus (STN) is the target of choice, as high-frequency stimulation in this nucleus improves all cardinal motor symptoms of PD, allowing a reduction of dopaminergic anti-Parkinson drug treatment (Fasano, Daniele, & Albanese, 2012). Although the exact mechanisms of DBS remain to be elucidated, it is assumed that STN stimulation alters electrical network activity within the cortico-subcortico-cortical networks, leading to an improvement of motor activity. As for a variety of other non-motor functions, the effects of DBS on language functions are variable, with studies showing improvement while others result in worsening of language functions. Castner et al. (2008) conducted a noun/verb generation task with STN stimulation on and off, where four probe-response settings were analysed using the procedure proposed by Peran et al. (2003). Every probe-response setting showed different results. They found an improvement of verb generation in the noun probe – verb response condition during STN stimulation, although the errors made during STN stimulation were associated with selection constraints. Because more errors were made when more competing alternative verbs were possible. This suggests that stimulation caused problems in lexical selection of competing alternatives. Noun generation was in turn negatively influenced by STN stimulation in the noun-noun condition, without being associated with selection constraints. Because PD patients performed significantly worse with stimulation than controls in both noun-noun condition and verb-verb condition, these deficits were attributed to a general word generation deficit. Phillips et al. (2012) demonstrated in their group of early-implanted PD patients that bilateral DBS stimulation improved naming of manipulated objects in reaction time, but not in accuracy. On the other hand, generation of regular verbs was negatively influenced by STN stimulation. In contrast with the above-mentioned studies, Silveri et al. (2012) found that STN stimulation improved overall word generation in naming, both with higher accuracy and with faster reaction times. DBS of the STN had a selective positive effect on spontaneous language production. Zanini et al. (2003) claimed that STN stimulation increased the amount of words and reduced morphosyntactic errors. They attributed this to a recovered equilibrium of the cortico-subcortical networks. In 2009, their findings were replicated and extended to include also morphosyntactic improvements after STN stimulation (Zanini et al., 2009).

DBS offers the opportunity to assess the effects of unilateral stimulation of the basal ganglia structures (Castner et al., 2007). The evaluation of unilateral stimulation effects on language can be particularly interesting because the cortical representation of language is strongly lateralized to the left hemisphere, especially for syntax (Dominey & Inui, 2009; Lindell, 2006; Menenti, Segaert, & Hagoort, 2012). In addition, several theoretical subcortical language models emphasize the specific involvement of left cortico-subcortical networks in language processes (Dominey & Inui, 2009; Friederici, 2011; Ullman, 2004).

PD is characterized by an asymmetric degeneration of dopaminergic depletion, resulting in lateralized motor symptomatology. The effect of an asymmetric degeneration of nigrostriatal projections and language has rarely been examined independent of general studies on cognition (Verreyt, Nys, Santens, & Vingerhoets, 2011). Holtgraves, McNamara, Cappaert, and Durso (2010) assessed the linguistic complexity of spontaneous language production by measuring sentence length and the proportion of function words and verbs. Patients with predominant right hemispheric dopaminergic depletion were found to produce significantly fewer verbs and more simplified linguistic output than patients with predominant left hemispheric dopamine depletion. Because pragmatic processes are more closely related to dopaminergic networks connected to the right frontal lobe (Jung-Beeman, 2005), they concluded that decreased linguistic complexity is a reflection of a pragmatic deficit associated with right frontal lobe dysfunction (Holtgraves et al., 2010). In another study an electrophysiological investigation was conducted on semantic comprehension of action words (De Letter, Van Borsel, & Santens, 2012). The current densities in ten predefined brain areas were measured during a covert word-reading task, on and off Levodopa administration. An increase of neural activity for semantic processing was found after Levodopa intake. Normally a bilateral symmetric distribution would be expected in healthy controls, but for some subjects the cortical activity was strongly lateralized. However, none of the patients described had higher dopamine sensitivity in the most dopaminergic depleted hemisphere, suggesting a larger dopamine-related effect on cognitive networks in the less affected hemisphere. In conclusion, both studies emphasize the different involvement of both hemispheres, reflecting asymmetrical alterations in linguistic processing related to the asymmetric degeneration of dopaminergic depletion. Together the asymmetric representation of language and the asymmetric degeneration of dopamine depletion, provide sufficient arguments to evaluate the effect of unilateral STN stimulation. To our knowledge, Schulz et al. (2012) were the first to examine language outcomes after unilateral stimulation of the STN. They assessed sentence comprehension and phonologic and semantic verbal fluency in four stimulation conditions. Bilateral stimulation deteriorated all linguistic measurements, relative to no stimulation. Left unilateral stimulation resulted in linguistic outcomes that were inferior to those obtained by right STN stimulation. These results were related to lateralization of cognitive functions (verbal memory, lexical selection, switching and serial ordering) and to the fact that stimulation parameters are generally tuned to optimal motor responses, instead of cognitive and linguistic functioning.

Up to now, no study has been reported that examined the effects of unilateral stimulation on spontaneous language production. In this report, it is our aim to assess linguistic performance in spontaneous speech after lateralized STN stimulation in PD, offering complementary evidence to Schulz et al., 2012, who used specific structured language paradigms. We wanted to answer the following research questions.

1. Does the spontaneous language production of PD differ semantically and morphosyntactically from that of normal subjects in any of the stimulation conditions?
2. Are any linguistic (semantic or morphosyntactic) effects of STN-DBS related to lateralization of stimulation?

Methods

Patients

Ten men (mean age 56 years, range 41-71 years) with advanced idiopathic PD as defined by Gelb, Oliver, and Gilman (1999) were included in this study. They were all considered appropriate candidates for bilateral STN stimulation because of severe and fluctuating symptomatology affecting quality of life. Before surgery, all subjects underwent intensive neurological and neuropsychological testing. Clinical assessment and magnetic resonance imaging (MRI) indicated that there were no co-morbid neurological diseases. Neuropsychological assessment revealed no signs of dementia or major depression. None of the patients had a history of psychiatric disorders or substance abuse. Asymmetric motor symptom predominance was defined as the agreement of the motor scores of the UPDRS, the clinical diagnosis of the neurologist and the patient’s subjective feelings of motor asymmetry. The clinical and demographic features are further described in Table 5.1. To ensure that nobody had developed dementia since DBS surgery, all patients were screened using Montreal Cognitive Assessment (MOCA)

(Dalrymple-Alford et al., 2010) before inclusion in this study. The stimulation parameters of each subject are summarized in Table 5.2.

Table 5.1 Medical and demographic features of PD patients (adapted).

Patient	Age (years)	PD duration (years)	DBS duration (months)	Motor symptoms predominance	Hand preference [a]	Language predominance [b]	NSVO-Z [c]	MOCA [d]
1	66	13	5	Right	10	Left	95%	23
2	58	10	37	Right	10	Left	99%	21
3	71	19	35	Right	10	Left	100%	27
4	56	16	12	Right	10	Left	98%	25
5	57	16	93	Right	10	Left	83%	27
6	54	10	20	Right	10	Left	98%	21
7	47	12	5	Left	10	Left	96%	25
8	57	14	7	Left	-1	Left	98%	25
9	41	13	106	Left	-6	Left	86%	23
10	57	14	65	Left	10	Left	83%	22
GA SD	56 (8.44)	14 (2.79)	39 (37.30)				0.94 (0.07)	24 (2.23)

Legend: [a] Hand preference is measured with the Dutch Handedness inventory (Van Strien, 1992) [b] Hemispheric language dominance is defined with the dichotic listening task; [c] NSVO-Z = the Dutch Intelligibility Assessment at sentence level (Martens, H., Van Nuffelen, G. & De Bodt M., 2010). [d] MOCA = Montreal Cognitive Assessment (Dalrymple-Alford et al., 2010); GA = group average; SD= standard deviation.

Neurosurgery

The neurosurgical placement of electrodes in the STN was done using a conventional stereotactic technique, with indirect targeting combining atlas coordinates, micro-electrode recording, and intra-operative macro-electrode stimulation to determine optimal location of stimulation contacts. Quadripolar electrodes (Medtronic 3389, Medtronic, Minneapolis) were implanted and external stimulation was done for at least one week before implantation and connection to the pulse generator in the abdominal wall.

Table 5.2 Summary of the individual stimulation parameters (adapted).

Patient	Left stimulator				Right stimulator			
	Pole	Ampl (V)	Pulse width (µs)	Freq (Hz)	Pole	Ampl (V)	Pulse width (µs)	Freq (Hz)
1	1- case +	1,8	90	130	9- case +	2,2	90	130
2	1-2+	4,5	90	130	5- case +	4	90	130
3	3- case+	3,7	90	130	6+7-	2,5	60	130
4	2-3-	2,5	90	130	9-10-11+	2,7	90	130
5	1-2+	5,3	90	130	7+6-5-	5	90	130
6	2-3- case+	1,8	90	130	8+9-10-11+	3	90	130
7	0- 1-	2,2	90	130	10-11-	2,6	90	130
8	1- case +	3	60	130	9- case +	3	60	130
9	1-2-	2	90	130	2- case +	1,1	60	130
10	3+2-	4	90	130	7+6-	4,3	90	130
GA SD		3,1 1.2	87 9.5			3.4 1.1	81 14.5	

Legend: Ampl = amplitude; Freq = frequency; GA = group average; SD= standard deviation.

Neurolinguistic analysis

Patients were all native Dutch speakers, who reported no premorbid language disorders, vision or hearing problems. Handedness was determined by the Dutch Handedness inventory (Van Strien, 1992) for which scores may range from -10 for extreme left-handedness until +10 for extreme right-handedness: eight patients were completely right-handed (+10), one moderately left-handed (-6) and one ambidextrous (-1). The hemispheric language predominance was defined by means of a dichotic listening task (Kimura, 1961).

The speech intelligibility of all subjects was judged using the "Nederlandstalig spraakverstaanbaarheidsonderzoek zinsniveau" (NSVO-Z), the Dutch version of "Dutch Intelligibility Assessment at sentence level" (DIA-S) (Martens, Van Nuffelen, Van den Putte, Wuyts, & De Bodt, 2010), in order to verify that speech intelligibility was not an interfering factor for reliable transcriptions of the language samples. NSVO-Z is a computer program that randomly selects 18 nonsense sentences from a database containing 1200 sentences, blinded from the test evaluator. The subject was asked to read the sentences aloud while being recorded. Next, all sentences were transcribed and compared to the target sentences. The intelligibility score was calculated as the percentage of correctly identified words. For people under the age of 70, a score lower than 96% is considered to be dysarthric. Above the age of 70, a score below 93.1% is labelled dysarthric. Subjects with a NSVO-Z score lower than 80% were excluded from this study.

The language analysis were based on a standardized method for quantitative analysis of spontaneous language production from the 'Analysis of Spontaneous Speech in Aphasia' (ASTA) (Boxum, van der Scheer, & Zwaga, 2010) in order to be able to refer to the normative data of the ASTA (van der Scheer, Zwaga, & Jonkers, 2011). The ASTA describes how to collect, transcribe and analyse language sample. The language samples are obtained by means of a semi-standardized interview without time constraints. The subjects had to answer open-ended autobiographical questions. The questions were referring to topics such as work, family and housing, traveling, leisure and general interests. At least three different topics were addressed during one interview. The first 300 words of each interview were orthographically transcribed for analysis.

Semantic analyses were conducted by counting the amount of nouns, the amount of lexical verbs, the variety of nouns, and the variety of lexical verbs (type-token ratio). Morphosyntactic evaluation was conducted by counting the amount of copula and modal verbs, mean length of utterance (MLU), percentage of correct sentences and finiteness index (proportion of correctly inflected verbs on the total number of clauses containing a verb).

In order to be able to interpret the results of the present study, some knowledge about syntactic construction of the Dutch language is required. In Dutch, copula and modal verbs are highly frequent and irregular verbs. They are accounted as closed-class words that contain hardly any lexical information (Bastiaanse, 2011). Lexical verbs are open-class words that have a lexical and a grammatical function in a sentence, determining the sentence structure and relationships with time and agreement (Altmann & Troche, 2011).

All transcriptions and analyses were independently done by two experienced speech pathologists. Subsequently, the results were compared and consensus was reached mutually in case of a discrepant judgment. The patients were assessed in four STN stimulation conditions: bilateral stimulation on, bilateral stimulation off, only stimulation of the left STN, only stimulation of the right STN. To avoid order or sequence effects within subjects, conditions were randomized. The patients maintained their optimal doses of medication during testing. After switching to a new stimulation condition, there was at least a fifteen-minute break to ensure the patient was adapted to the new condition and motor effects of stimulation changes were visible. Stimulation parameters were those for which the subjects experienced optimal clinical benefits. All audio samples were recorded digitally on a notebook (Dell Latitude e6500) using a condenser stereo microphone (Sony ECM-MS907) and the acoustic software Praat (Boersma, 2002). Recording took place in a quiet room without distractions. Patients were aware of the study aims and agreed by signing an informed consent. This study was approved by the Ethical Committee of Ghent University.

Statistical analysis

All statistical analyses were performed in SPSS 21 for Windows. Normal distribution of the dataset was visually explored with Q-Q plots and confirmed by a Kolmogorov-Smirnov test. The linguistic measures of our PD group in the four stimulation conditions were compared with the normative data of the ASTA via a one-sample *t* test. P-values less than 0.05 were considered to be significant. The linguistic variables in the four stimulation conditions were compared with each other using a linear mixed model. Due to multiple comparisons, a Bonferroni correction was applied in the linear mixed model whereby P-values less than .006 were considered significant.

Results

A summary of the results of the Dutch Handedness inventory, the NSVO-Z and the dichotic listening task can be found in Table 5.1.

Linguistic characteristics of spontaneous language production in PD in the four stimulation conditions

To obtain an overall impression of the linguistic characteristics of spontaneous language production in PD, all linguistic variables of our PD group were compared for each stimulation condition with the normative means of the ASTA (Table 5.3).

When comparing the mean results of the different stimulation conditions to normative means, the condition with STN stimulation off gave the largest amount of deviant linguistic parameters. PD patients produced significantly fewer nouns and there was a larger diversity of lexical verbs in the condition ‘STN stimulation off’. On top, all syntactic variables deviated from normative values of the ASTA in the condition ‘STN stimulation off’. The PD group generated, in the condition with STN stimulation off, significantly more copula and modal verbs. The MLU was smaller and the amount of correct sentences reduced. Finally, the finiteness index was lower than the normative value.

The condition with bilateral STN stimulation resulted in a deviation from normative means in terms of a lower production of nouns, a lower percentage of correct sentences, and a lower finiteness index. In the condition with only stimulation of the left STN, a lower amount of nouns, a higher amount of copula and modal verbs, a lower percentage of correct sentences and a lower finiteness index, were registered compared to normative values. Finally, in the condition with stimulation of the right STN only a lower percentage of correct sentences in comparison to the normative data was found.

Table 5.3 Descriptive data of the overall PD group, the mean score of the ASTA normative data and the results of the on sample t-test in all stimulation conditions.

	Stimulation condition	Mean ASTA	Mean PD	Stand. Dev	t	p		95% Confidence Interval of the Difference	
								Lower	Upper
Amount of nouns	Bilateral off	48	40,4	9,82	-2,447	,037	*	-14,6269	-,5731
	Bilateral on	48	43,2	6,55	-2,319	,046	*	-9,4824	-,1176
	Only left	48	39,3	6,14	-4,475	,002	*	-13,0975	-4,3025
	Only right	48	43,7	9,76	-1,393	,197		-11,2851	2,6851
TTR nouns	Bilateral off	,76	,748	,126	-,301	,770		-,1022	,0782
	Bilateral on	,76	,736	,105	-,720	,490		-,0994	,0514
	Only left	,76	,784	,074	1,032	,329		-,0286	,0766
	Only right	,76	,746	,107	-,415	,688		-,0904	,0624
Amount of lexical verbs	Bilateral off	29	28,3	4,42	-,500	,629		-3,8643	2,4643
	Bilateral on	29	29,1	5,15	,061	,952		-3,5856	3,7856
	Only left	29	29,2	4,73	,134	,897		-3,1857	3,5857
	Only right	29	30,5	5,95	,797	,446		-2,7556	5,7556
TTR lexical verbs	Bilateral off	,63	,716	,074	3,684	,005	*	,0332	,1388
	Bilateral on	,63	,659	,043	2,142	,061		-,0016	,0596
	Only left	,63	,678	,124	1,226	,251		-,0406	,1366
	Only right	,63	,683	,157	1,064	,315		-,0597	,1657
Amount of copula and modal verbs	Bilateral off	12	16,6	6,11	2,379	,041	*	,2265	8,9735
	Bilateral on	12	15,1	5,95	1,647	,134		-1,1582	7,3582
	Only left	12	18,5	4,33	4,750	,001	*	3,4047	9,5953
	Only right	12	13,6	5,04	1,004	,341		-2,0037	5,2037
MLU	Bilateral off	8,63	7,17	,924	-4,982	,001	*	-2,1172	-,7948
	Bilateral on	8,63	7,94	2,11	-1,029	,330		-2,1999	,8239
	Only left	8,63	7,99	,943	-2,152	,060		-1,3170	,0330
	Only right	8,63	7,56	2,18	-1,543	,157		-2,6285	,4965
% correct sentences	Bilateral off	,93	,717	,149	-4,532	,001	*	-,3193	-,1067
	Bilateral on	,93	,751	,056	-10,096	,000	*	-,2191	-,1389
	Only left	,93	,689	,122	-6,234	,000	*	-,3284	-,1536
	Only right	,93	,723	,128	-5,122	,001	*	-,2984	-,1156
Finiteness index	Bilateral off	,99	,949	,024	-5,388	,000	*	-,0590	-,0241
	Bilateral on	,99	,942	,055	-2,739	,023	*	-,0875	-,0083
	Only left	,99	,953	,024	-4,795	,001	*	-,0538	-,0193
	Only right	,99	,961	,057	-1,607	,142		-,0703	,0119

Legend: TTR = type token ratio; % correct sentences = percentage of correct sentences; MLU = mean length of utterance; Stand. Dev = standard deviation.* $p < 0.05$.

Effects of stimulation

In terms of stimulation effects, none of the linguistic variables varied significantly across the four stimulation conditions (Table 5.4).

Table 5.4 Comparison of linguistic variables in the different stimulation conditions (Linear mixed model).

Differences in stimulation conditions	p-value
Amount of nouns	.564
Type token ratio nouns	.706
Amount of lexical verbs	.771
Type token ratio lexical verbs	.628
Amount of copula and modal verbs	.190
MLU	.537
Percentage correct sentences	.486
Finiteness index	.687

Legend: MLU, mean length of utterance.

Discussion

The present study aimed to provide a more detailed description of the linguistic features of spontaneous language production in PD, under different STN stimulation conditions.

Linguistic characteristics of spontaneous language production in PD (STN stimulation off)

The current study corroborates previous research findings (Illes et al., 1988; Zanini et al., 2009; Zanini et al., 2010) indicating an overall morphosyntactic deficit. PD patients produced shorter and more incorrect sentences than healthy subjects. A smaller MLU indicates a reduction in grammatical complexity (Borovsky, Saygin, Bates, & Dronkers, 2007; Murray, 2000), supporting the suggestion that the cortico-basal ganglia-thalamocortical loops are involved in the processing of complex and ambiguous sentences (Dominey & Inui, 2009).

Although the amount of nouns is usually seen as a semantic parameter, the reduced amount of nouns can be explained in terms of their grammatical function (Grossman et al., 2003; Peran et al., 2003). Nouns obtain a thematic role in a grammatical structure and can be partially replaced by function words, which are close class words. This is in contrast with verbs who have a dominant role in sentence generation and function as an assigner of thematic roles (Altmann & Troche, 2011). Sentences are built around verbs. Therefore, the vast majority of sentences in spontaneous language production have to include a verb. It has been suggested that in order to be able to assign thematic roles, patterns of activity within a recurrent prefrontal network are necessary (Bates, McNew, Macwhinney, Devescovi, & Smith, 1982; Dominey & Inui, 2009). The resulting patterns need to be encoded by the striatum to map open class elements, like nouns, onto their appropriate thematic roles (Hinaut & Dominey, 2013). Reduced noun production can therefore be the result of morphosyntactic difficulties due to dysfunctional cortico-basal ganglia-thalamocortical networks.

The reduced amount of nouns is in contrast with a previous study on the use of nouns and verbs in spontaneous language production (Pignatti et al., 2006), where no differences between PD and healthy controls were found. The discrepancies between the outcomes of both studies are difficult to explain, as the methodologies are quite similar. The lack of more detailed information on the PD population in the Pignatti et al. (2006) study precludes a full comparison of both reports.

To our knowledge, the present study is the first study dissociating lexical verbs from copula and modal verbs in PD language analysis. Also the enlarged use of copula and modals confirms the presence of morphosyntactic difficulties. By replacing lexical verbs by high frequent, irregular, non-lexical verbs, PD patients avoid inflection of lexical verbs. Verb inflection deficits in PD have been described before and the diminished finiteness index supports the idea of verb inflection deficits (Colman et al., 2009; Longworth et al., 2005; Ullman et al., 1997). On the other hand, because copular and modal verbs are grammatical close class words, the overuse can be a compensatory mechanism to facilitate grammatical role assignment and postpone the mapping of open class words onto the grammatical structure to the rear end of that grammatical structure (Bastiaanse, 2011; Hinaut & Dominey, 2013).

Beside the morphosyntactic deficits, the spontaneous language production is probably influenced by more general cognitive dysfunctions. The increased variety of lexical verbs can be explained in that perspective. A possible underlying cause of language disturbances in PD studies is the impairment in inhibition and selection of competing alternatives. Because verbs have more lexical alternatives than nouns, they are probably more vulnerable to inhibitory disturbances (Peran et al., 2003). The suppression and selection of irrelevant and relevant alternatives demands balanced levels of dopamine, not only in the striatum but also in the prefrontal cortex. Imbalance within cortico-basal ganglia-thalamocortical circuits can lead to a disturbance of competition and inhibition (Crescentini et al., 2008; Fallon, Williams-Gray, Barker, Owen, & Hampshire, 2013; Silveri et al., 2012), causing increased competition among lexical verbs in PD.

Effects of stimulation

No consistent differences were found between stimulation conditions across the different linguistic parameters. Despite the fact that no stimulation interactions were statistically detectable, the mean scores of the linguistic parameters clearly deviate from the normative values, depending on the stimulation condition. This does not rule out the possibility that spontaneous language production might be influenced by stimulation effects, but perhaps these effects are averaged out, due to additional variables (e.g. demographic and medical parameters) that interact with the effect of STN stimulation of each PD patient. Some of the demographic characteristics of the study group were heterogeneous, like disease duration and time, they have been receiving STN stimulation. Although all patients were in a stable condition after DBS surgery and the selection criteria to receive DBS surgery were applied strictly, it cannot be excluded that it can influence outcome. However, at the present there are no long-term data available to refute or confirm the influences of these variables.

One of the variables that possibly interacts with the linguistic outcome is the lateralization of the nigrostriatal degeneration. In this study, the asymmetric characteristic of PD is not taken into account and both PD patients with primarily left-sided and right-sided motor disturbances were included in this study. Prior studies found a correlation between the asymmetric degeneration of nigrostriatal networks and the strongly lateralised cortical representation of language (De Letter et al., 2012; Holtgraves et al., 2010).

In addition, stimulation parameters are known to influence the outcome of DBS. Stimulation parameters that are beneficial for motor function, which are of primary interest for the treating physicians, do not necessarily correspond to the optimal parameters for cognitive function or speech (Hershey et al., 2008; Tripoliti et al., 2008). Another consideration is that the localization of the electrode within the STN, with a resulting effect on different somatotopically arranged areas within the motor part of the STN, can influence the results (Tripoliti et al., 2008).

Although the different stimulation conditions only results in deviations compared to normative data and interpretation should be done with care, these explorative data may provide indications and suggestions for further research.

The highest number of linguistic variables outside the range of healthy control were found in the off-stimulation condition, suggesting that linguistic deficits might be inherent to PD pathology. Furthermore, STN stimulation improves the spontaneous language production, regardless of the stimulation condition. Yet, the effect of STN stimulation varies depending on the measured linguistic parameter indicating that the linguistic deviations are caused by different underlying mechanisms. First, it confirms the idea that DBS stimulation is task-specific and the outflow pathways are affected differently depending on the task (Schulz et al., 2012; Thobois & Broussolle, 2012; Thobois et al., 2007). Second, it stresses the complex interplay of linguistic and non-linguistic elements in spontaneous language production.

No studies have been performed on the lateralized effect of STN stimulation on spontaneous language production. Our data indicate that there seems to be an effect on some linguistic outcomes, depending on the side of stimulation. Stimulation of the left STN results in less morphosyntactically correct sentences with more modals and copula, less nouns and more mistakes in verb inflection in comparison with the conditions “bilateral stimulation on” and “only stimulation of the right STN”. For all subjects, the left hemisphere was assigned to be the language dominant one. It has been suggested that STN stimulation has a negative effect on the hemisphere specific language functions (Holtgraves et al., 2010). The negative effect of the left STN is parallel with findings on speech disturbances (Santens, De Letter, Van Borsel, De Reuck, & Caemaert, 2003; Tripoliti et al., 2011), and previous linguistic work (Schulz et al., 2012). Stimulation of the left STN seems to interfere with left (sub)cortical networks which are largely associated with morphosyntactic functions (Friederici, Kotz, Werheid, Hein, & von Cramon, 2003; Kotz, Schwartze, & Schmidt-Kassow, 2009). Once the right STN is stimulated as well, language production seems to normalize. When the right STN is stimulated alone, all parameters normalize except the percentage of correct sentence. This is consistent with the idea that the left basal ganglia are involved in syntactic processes (Dominey & Inui, 2009).

Conclusion

The spontaneous language production of PD patients contains more morphosyntactic errors than healthy subject. The effect of STN stimulation seems to be highly individual. The findings of this study are a confirmation of the complexity of language disturbances in PD. It underscores once again the multifactorial interaction of cortical and subcortical structures in semantic and syntactic aspects of production and the long road ahead to unravel these processes. Further research will need to focus on disentangling all influencing factors, with a special emphasis on laterality of cortico-subcortical effects in spontaneous language production.

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Subthalamic nucleus stimulation and spontaneous language production in Parkinson's disease: a double laterality problem

CHAPTER 6

Batens, K., De Letter, M., Raedt, R., Duyck, W., Vanhoutte, S., Van Roost, D., & Santens, P. (2015). Subthalamic nucleus stimulation and spontaneous language production in Parkinson's disease: a double laterality problem. *Brain and language, 147,* 76-84.

Abstract

Background: Asymmetric degeneration of dopaminergic neurons~~,~~ are characteristic for Parkinson's disease (PD). Despite the lateralized representation of language, the correlation of asymmetric degeneration of nigrostriatal networks in PD with language performance has scarcely been examined.

Objective/Hypothesis: The laterality of dopamine depletion influences language deficits in PD and thus modulates the effects of subthalamic nucleus (STN) stimulation on language production.

Methods: The spontaneous language production of patients with predominant dopamine depletion of the left (PD-left) and right (PD-right) hemisphere was compared in four stimulation conditions.

Results: PD-right made comparatively more verb inflection errors than PD-left. Bilateral STN stimulation improves spontaneous language production only for PD–left.

Conclusions: The laterality of dopamine depletion influences spontaneous language production and the effect of STN stimulation on linguistic functions. However, it is probably only one of the many variables influencing the effect of STN stimulation on language production.

Highlights

- The laterality of dopamine depletion influences spontaneous language production
- Bilateral STN stimulation improves language production only for left side depletion.
- There are likely other variables influencing the effect of DBS on language production

Keywords

Parkinson's disease; lateralization of linguistic functions; deep brain stimulation; spontaneous language production; asymmetric dopamine depletion

Introduction

There is an increasing evidence for subcortical involvement in language processes (Chan, Ryan, & Bever, 2011; De Letter, Van Borsel, & Santens, 2012; Robles, Gatignol, Capelle, Mitchell, & Duffau, 2005). However, it is still a matter of debate whether these linguistic functions are processed in subcortical structures themselves or rather in a network encompassing cortical and subcortical areas.

A hallmark of PD is the asymmetry of motor symptoms, which reflects the asymmetric degeneration of dopaminergic neurons (Djaldetti, Ziv, & Melamed, 2006; Kempster, Gibb, Stern, & Lees, 1989). This unilateral predominance of symptoms is generally noticeable throughout the course of the disease, even long after the disease becomes clinically bilateral (Antonini et al., 1995; Cronin-Golomb, 2010; Djaldetti et al., 2006). The brain tries to mitigate the dopamine deficiencies with compensatory neural responses. Compensatory mechanisms that have been described are: expansion of activated cortical areas, increased excitability of cortical areas, and involvement of contralateral hemisphere (Kojovic et al., 2012; Spagnolo et al., 2013). This compensatory reorganisation can influence the interhemispheric balance (Spagnolo et al., 2013). In motor tasks, the lateralized dopamine deficits are compensated by expanding the normal motor network to areas that are usually only activated in complex movements and/or by increasing the excitability of motor areas. In early PD, this increased excitability is only present in the most affected hemisphere, creating an imbalance between both hemispheres. As PD advances, this imbalance disappears, due to an increased excitability of both hemispheres (Spagnolo et al., 2013).

Although motor problems are the most visible lateralized symptoms, asymmetric degeneration also affects non-motor and cognitive functions (Cubo, Martinez Martín, Martin-Gonzalez, Rodríguez-Blázquez, & Kulisevsky, 2010; Kempster, Gibb, Stern, & Lees, 1989; Riederer & Sian-Hülsmann, 2012; Verreyt, Nys, Santens, & Vingerhoets, 2011). For example, difficulties with orientation, mental imagery, and visuospatial attention are observed in PD patients with more severe right-hemispheric dopamine depletion. On the other hand, problems in verbal memory are more associated with profound nigrostriatal degeneration in the left hemisphere. Studies examining executive functions lead to an equivocal answer with respect to asymmetry (Verreyt et al., 2011).

The cortical representation of syntactic language functions is strongly lateralized to the left hemisphere, whereas semantic~~s~~ functions are more bilaterally represented (Dominey & Inui, 2009; Lindell, 2006; Menenti, Segaert, & Hagoort, 2012). Despite this lateralized representation of language, the correlation of asymmetric degeneration of nigrostriatal networks and language has rarely been examined, merely as a subpart in general cognitive studies (Verreyt et al., 2011). Holtgraves, McNamara, Cappaert, and Durso (2010) assessed the linguistic complexity of spontaneous language production by measuring sentence length and the proportion of function words and verbs. Patients with more severe right-hemispheric dopamine depletion were found to produce significantly fewer verbs and more simplified linguistic output than patients with more severe left-hemispheric dopamine depletion. Because pragmatic processes are closely related and associated with dopaminergic networks of the right frontal lobe, Holtgraves et al. (2010) suggested that decreased linguistic complexity reflects a pragmatic deficit of the right frontal cortex. A second study reported an electrophysiological investigation on semantic comprehension of action words (De Letter et al., 2012). The current densities in ten predefined brain areas were measured during a covert word-reading task, on and off Levodopa administration. An increase of neural activity for semantic processing was found after Levodopa intake. Normally, a bilateral distribution would be expected in healthy controls, but in some subjects, the cortical activity was strongly lateralized. However, none of the patients described had higher dopamine sensitivity in the most affected hemisphere, suggesting a larger dopamine-related effect on cognitive networks in the less affected hemisphere.

Deep Brain Stimulation (DBS) has become an established therapeutic option for advanced PD with motor fluctuations that are refractory to medical treatment (Kleiner-Fisman et al., 2006; Klostermann, Krugel, & Wahl, 2012). At present, in most centres performing DBS, the subthalamic nucleus (STN) is the target of choice, as high-frequency stimulation in this nucleus improves all cardinal motor symptoms of PD, allowing a reduction of dopaminergic anti-Parkinson drug treatment (Fasano, Daniele, & Albanese, 2012). Although the working mechanism of DBS is still unclear, DBS is presumed to override the oscillatory patterns of the disrupted networks (Benabid et al., 1996; McIntyre & Hahn, 2010). The effect of STN stimulation on language variables is not as straightforward as on motor symptoms (Klostermann et al., 2012). Whelan, Murdoch, Theodoros, Hall, and Silburn (2003) were among the first to assess the effect of STN stimulation on different high-level language functions with a large assessment battery. Some linguistic functions improved, whereas some others deteriorated with STN stimulation. These contradictory results were also found in word generation studies (Castner et al., 2008; Silveri et al., 2012) and studies examining syntactic functions (Homer, Rubin, Horowitz, & Richter, 2012; Zanini et al., 2003; Zanini et al., 2009).

The divergent DBS results indicate that various neural circuits within the STN have different physiological functions (McIntyre & Hahn, 2010; Temel, Blokland, Steinbusch, & Visser-Vandewalle, 2005; Thobois & Broussolle, 2012). Therefore, the optimal DBS stimulation parameters for motor results might not be the same as those for language or other cognitive functions.

Furthermore, DBS is an interesting method to assess the effects of unilateral STN stimulation on the dopaminergic network, especially because of the asymmetry in dopamine degeneration (Castner et al., 2007). In contrast to speech, the effects of unilateral STN stimulation on language have been rarely tested and no research has been done on the interaction of DBS with asymmetric dopamine depletion in language tasks. One study reporting the lateralized effects of STN stimulation on language outcomes, yielded worse linguistic outcome of left STN stimulation compared to stimulation of the right STN (Schulz et al., 2012). The authors hypothesized that the negative influence of bilateral stimulation on language function likely originates from stimulation of the left STN. The discrepancy between stimulation of the right and left STN was associated with the lateralization of linguistic functions. In a recent study (Batens et al., 2014) we investigated the effect of STN stimulation on spontaneous language production in four stimulation conditions (bilateral stimulation on, bilateral stimulation off, stimulation of the left STN only, stimulation of the right STN only). No significant differences between stimulation conditions were found, despite the linguistic differences with normal controls. We concluded that the effects of STN stimulation on spontaneous language production were highly individual, reflecting a complex interplay of multiple factors of which lateralization of the nigrostriatal degeneration is one.

To obtain a better understanding of the factors underlying language production in PD and the effect that DBS has on linguistic processing, we assessed the interaction between DBS and asymmetric dopamine depletion on linguistic outcomes. No previous studies have addressed this issue.

The aim of this study was to investigate the interaction between DBS and asymmetric dopamine depletion on linguistic outcomes in patients with PD, answering the following specific research questions:

1. Does asymmetric dopamine depletion influence semantic and morphosyntactic aspects of spontaneous language production of PD?
2. Does STN stimulation interact with the side of predominant dopamine depletion in the production of spontaneous language?

Methods

Patients

Fourteen participants in the advanced stage of idiopathic PD (following the definition of Gelb, Oliver, and Gilman, 1999) were included in this study. They were all considered appropriate candidates for STN stimulation because of severe and fluctuating symptoms that affected the quality of life. Before surgery, all subjects underwent intensive neurological and neuropsychological testing. Clinical assessment and magnetic resonance imaging (MRI) indicated that there were no co-morbid neurological diseases. Neuropsychological assessment revealed no signs of dementia or major depression. None of the patients had a history of psychiatric disorders or substance abuse.

The subjects were divided into two groups depending on the lateralization of motor symptoms. Seven patients had primarily left-sided motor disturbances reflecting predominant right hemispheric dopamine depletion (PD-right). The other seven PD patients had primarily right-sided motor disturbances with predominant left hemispheric dopamine depletion (PD-left). Motor symptom predominance was agreed upon by the motor scores of the UPDRS, the clinical evaluation of the neurologist, and the patient's subjective feelings of motor asymmetry. To ensure that nobody had developed dementia since DBS surgery, all patients were screened using Montreal Cognitive Assessment (MOCA) (Dalrymple-Alford et al., 2010) before inclusion in this study. The clinical and demographic features are further described in Table 6.1. The stimulation parameters of each subject are summarized in Table 6.2. Both groups did not differ significantly from each other concerning age, duration of PD, duration of DBS and amplitude of stimulation.

Table 6.1 Medical and demographic features of PD patients (adapted).

Patient		Age (years)*	Hand preference [a]	language predominance [b]	Motor symptoms predominance	PD duration (years)°	DBS duration (months)°	NSVO-Z [c]	MOCA [d]
1		66	10	Left	Right	13	6	95%*	23
2		58	10	Left	Right	10	37	99%	21
3		71	10	Left	Right	19	35	100%	27
4		56	10	Left	Right	16	12	98%	25
5		57	10	Left	Right	16	93	83%*	27
6		54	10	Left	Right	10	20	98%	21
7		71	10	Left	Right	15	40	98%	23
Motor right	GA SD	61.85 7.29				14.14 3.34	34.71 28.83	0.96 0.06	23.86 2.54
8		47	10	Left	Left	12	3	96%	25
9		57	-1	Left	Left	14	7	98%	25
10		41	-6	Left	Left	13	106	86%*	23
11		57	10	Left	Left	14	65	83%*	22
12		60	-3	Left	Left	14	36	90%*	26
13		73	9	Left	Left	15	87	98%	21
14		53	10	Left	Left	16	80	87%*	28
Motor left	GA SD	55.43 10.16				14 1.29	54.86 40.24	0.91 0.06	24.29 2.43
GA SD		58.64 9.12				14.07 2.43	44.79 35.22	0.98 0.06	24.07 2.40

Legend: [a] Hand preference is measured with the Dutch Handedness inventory, scores may range from -10 for extreme left-handedness until +10 for extreme right-handedness (Van Strien, 1992); [b] Hemispheric language dominance is defined with the dichotic listening task; [c] NSVO-Z = the Dutch Intelligibility Assessment at sentence level (Martens, Van Nuffelen, Van den Putte, Wuyts, & De Bodt, 2010); *a score lower than 96% is considered to be dysarthric for people under the age of 70; [d] MOCA = Montreal Cognitive Assessment (Dalrymple-Alford et al., 2010); GA = group average; SD= standard deviation; motor right= motor symptoms predominance right; motor left= motor symptoms predominance left; ° at the time of inclusion.

Neurosurgery

The neurosurgical placement of electrodes in the STN was done using a conventional stereotactic technique with indirect targeting, combining atlas coordinates, micro-electrode recording, and intra-operative macro-electrode stimulation to determine optimal location of stimulation contacts. Quadripolar electrodes (Medtronic 3389, Medtronic, Minneapolis) were implanted and external stimulation was done for at least one week before implantation and connection to the pulse generator in the abdominal wall.

Table 6.2 Summary of the individual stimulation parameters (adapted).

PD-left								
Patient	Left stimulator				Right stimulator			
	Pole	Ampl (V)	Pulse width (µs)	Freq (Hz)	Pole	Ampl (V)	Pulse width (µs)	Freq (Hz)
1	1-case+	1.8	90	130	9-case+	2.2	90	130
2	1-2+	4.5	90	130	9-case+	4	90	130
3	3-case+	3.7	90	130	10+11-	2.5	60	130
4	2-3-	2.5	90	130	9-10-11+	2.7	90	130
5	1-2+	5.3	90	130	9-10-11+	5	90	130
6	2-3-case+	1.8	90	130	8+9-10-11+	3	90	130
7	0+1-2-3+	3.1	60	130	10-case+	3.1	60	130
GA		32.43	85.71			16.71	81.43	
SD		13.39	11.34			12.20	14.64	
PD-right								
Patient	Left stimulator				Right stimulator			
	Pole	Ampl (V)	Pulse width (µs)	Freq (Hz)	Pole	Ampl (V)	Pulse width (µs)	Freq (Hz)
8	0-1-	2.2	90	130	10-11-	2.6	90	130
9	1-case+	3	60	130	9-case+	3	60	130
10	1-2-	2	90	130	10-case+	1.1	60	130
11	3+2-	4	90	130	9-11+	4.3	90	130
12	1-case+	2.3	90	130	9-10-	2.3	90	130
13	1-2-	2.9	60	130	10-case+	3.3	60	130
14	2-case+	3.5	60	160	11-case+	2	60	160
GA		16.86	72.86			20.14	72.86	
SD		13.66	16.04			15.48	16.04	

Legend: PD-left= patient with predominantly left hemispheric dopamine depletion; PD-right= patient with predominantly right hemispheric dopamine depletion; Ampl = amplitude; Freq = frequency; GA = group average; SD= standard deviation.

Neurolinguistic analysis

Patients were all native Dutch speakers, who reported no premorbid language disorders, vision or hearing problems. Handedness was determined by the Dutch Handedness inventory (Van Strien, 1992) for which scores may range from -10 for extreme left-handedness to +10 for extreme right-handedness. Ten patients were completely right-handed (+10), one strongly right-handed (+9), one moderately left-handed (-6) and two ambidextrous (-1 and -3). In the PD-left group, all patients were right-handed. There were two ambidextrous persons and one left-handed person in the PD-right group. The hemispheric language predominance was defined by means of a dichotic listening task (Kimura, 1961) and indicated that the left hemisphere was the language dominant hemisphere for all PD patients.

The speech intelligibility of all subjects was judged using the "Nederlandstalig spraakverstaanbaarheidsonderzoek zinsniveau" (NSVO-Z), the Dutch version of "Dutch Intelligibility Assessment at sentence level" (DIA-S) (Martens, Van Nuffelen, Van den Putte, Wuyts, & De Bodt, 2010), in order to verify that speech intelligibility was not an interfering factor for reliable transcriptions of the language samples. NSVO-Z is a computer program that randomly selects 18 nonsense sentences from a database containing 1200 sentences, blinded from the test evaluator. The subject was asked to read the sentences aloud while being recorded. Next, all sentences were transcribed and compared to the target sentences. The intelligibility score was calculated as the percentage of correctly identified words. For people under the age of 70, a score lower than 96% is considered to be dysarthric. Above the age of 70, a score below 93.1% is labelled dysarthric. Subjects with a NSVO-Z score lower than 80% were excluded from this study. Based on the NSVO-Z results, two out of seven PD-left patients and four out of seven PD-right patients were labelled dysarthric.

The language analysis was conducted using the standardized method for quantitative analysis of spontaneous language production from the 'Analysis of Spontaneous Speech in Aphasia' (ASTA) (Boxum, van der Scheer, & Zwaga, 2010) in order to be able to refer to the normative data of the ASTA (van der Scheer, Zwaga, & Jonkers, 2011). The ASTA describes how to collect, transcribe and analyse spontaneous language samples. The language samples are obtained by means of a semi-standardized interview without time constraints. The subjects have to answer open-ended autobiographical questions. The questions were referring to topics such as work, family and housing, traveling, leisure and general interests. At least three different topics were addressed during one interview. The first 300 words of each interview were orthographically transcribed for analysis.

Semantic analyses were conducted by counting the number of nouns, lexical verbs and the variety of nouns and lexical verbs (type-token ratio). Type-token ratios were calculated by dividing the number of different nouns or lexical verbs by the total number of nouns or lexical verbs. Morphosyntactic evaluation was conducted by counting the number of copula and modal verbs, mean length of utterance (MLU), percentage of correct sentences and finiteness index (proportion of correctly inflected verbs divided by the total number of clauses containing a verb). In order to be able to interpret the results of the present study, some knowledge about syntactic construction of the Dutch language is required. In Dutch, copula and modal verbs are highly frequent and irregular verbs. They are accounted as closed-class words that contain hardly any lexical information (Bastiaanse, 2011). Lexical verbs are open-class words that have a lexical and a grammatical function in a sentence, determining the sentence structure and relationships with time and agreement (Altmann & Troche, 2011).

All transcriptions and analyses were independently done by two experienced speech pathologists, who were blinded from patients' dopamine depletion asymmetry and the STN stimulation condition. Subsequently the results were compared and mutual consensus was reached in case of a discrepant judgment.

The patients were assessed in four STN stimulation conditions: bilateral stimulation on, bilateral stimulation off, stimulation of the left STN only, stimulation of the right STN only. To avoid order or sequence effects within subjects, conditions were randomized. The patients maintained their optimal doses of medication during testing. All testing was conducted on the same day. After switching to a new stimulation condition, there was at least a fifteen-minute break to reassure that the patient was adapted to the new STN stimulation condition.

The audio samples were recorded digitally on a notebook (Dell Latitude E 6500) using a condenser stereo microphone (Sony ECM-MS907) and the acoustic software Praat (Boersma, 2002). Recording took place in a quiet room without distractions.

Patients were aware of the study aims and agreed to participate by signing an informed consent. This study was approved by the Ethical Committee of Ghent University.

Statistical analysis

All statistical analyses were performed in IBM SPSS Statistics 21 for windows. Significance level for all tests was set at ≤ .05. The linguistic measures of both PD groups in bilateral stimulation off were mutually compared by means of a Mann-Whitney test. In addition, the linguistic measures of both PD groups in all stimulation conditions were compared separately with the normative data of the ASTA via a one-sample *t* test.

The effect of STN stimulation on the linguistic variables of both PD groups were evaluated pairwise, bilateral stimulation on versus bilateral stimulation off and left simulation only versus right stimulation only , using mixed repeated measures ANOVA with stimulation condition as within-subject variable and asymmetric dopamine depletion as between-subjects factor. Post-hoc, each PD group was separately tested for main effects of stimulation using pairwise comparisons with Bonferroni correction. To substantiate the statistical result found in the comparison of left stimulation only versus right stimulation only for the number of copula and modal verbs, an additional Wilcoxon sign rank test was conducted to compare these stimulation effects for both PD groups separately.

Results

Linguistic difference depending on asymmetric dopamine depletion

In the mutual comparison of both PD groups the finiteness index was the only linguistic parameter that differed significantly (p= .049). PD-right had a significant lower finiteness index compared to PD-left.

To obtain an overall impression of the linguistic characteristics of the two PD groups separately in contrast with healthy subjects, all linguistic variables in the condition without STN stimulation were compared with the ASTA norms (Table 6.3). Both PD groups did not differ significantly from the normative data for the number of verbs and the type-token ratio of nouns. PD-left produced a significant lower number of nouns and had a higher type-token ratio of lexical verbs than the norm data. In contrast, PD-right only produced a significantly higher type-token ratio of lexical verbs. PD-left had a significantly lower MLU with an excessive number of copula and modal verbs. PD-right also had a significantly lower MLU but did not show increase of copula and modal verbs. Furthermore, the percentage of correct sentences and the finiteness index were, for both PD groups, significantly lower than the normative data.

Effects of STN stimulation depending on asymmetric dopamine depletion

In order to obtain a general overview, the linguistic variables were compared to normative values of the ASTA for both groups in each stimulation condition (Table 6.3). For the number of nouns the results per stimulation condition depended on the lateralization of PD. For PD-left, the number of nouns was beneath the normative data in the condition bilateral stimulation off, only stimulation of the left STN and only stimulation of the right STN. For PD-right, the number of nouns was beneath the normative data in the condition: bilateral stimulation on and only left STN stimulation. Type token ratio of nouns and number of lexical verbs were within the normative data in every stimulation condition for both PD-groups. Type-token ratio of lexical verbs was for both PD-groups only significant higher than normative data in the condition bilateral stimulation off. The number of copula and modal verbs for PD-left was significant higher than normative data in the conditions bilateral stimulation off and only stimulation of the left STN. The number of copula and modal verbs for PD-right remained within the normal range for all stimulation condition. MLU was significantly lower than normative data for PD-left in the conditions: bilateral stimulation off and stimulation of the left STN. For PD-right, MLU was significantly lower than normative data with bilateral stimulation on and off. The percentage of correct sentences remained for both PD-groups below the normative data, irrespective of the stimulation condition. Finally, the finiteness index was only within the normal range for PD-left when the right STN only

Table 6.3 Descriptive data of both PD groups, the mean score of the ASTA normative data and the results of the one sample t-test in all stimulation conditions.

	Stimulation condition	Mean ASTA	PD-left Mean PD	PD-left Stand. Dev	PD-left t	PD-left p	PD-right Mean PD	PD-right Stand. Dev	PD-right t	PD-right p
Number of nouns	Bilateral off	48	38.0	10.1	-2.633	.039*	40.3	11.47	-1.78	.125
	Bilateral on	48	45.1	6.44	-1.174	.285	36.3	10.00	-3.10	.021*
	Only left	48	39.0	5.16	-4.611	.004*	36.0	9.06	-3.51	.013*
	Only right	48	41.3	6.99	-2.540	.044*	40.3	13.19	-1.55	.173
TTR nouns	Bilateral off	.76	. 730	.130	-.611	.564	.801	.088	1.24	.261
	Bilateral on	.76	.733	.121	-.594	.574	.801	.082	1.33	.230
	Only left	.76	.811	.072	1.88	.109	.786	.068	1.00	.354
	Only right	.76	.809	.100	1.29	.246	.709	.091	-1.50	.185
Number of lexical verbs	Bilateral off	29	28.7	5.19	-.146	.889	26.7	3.73	-1.62	.156
	Bilateral on	29	28.3	4.57	-.413	.694	29.3	4.99	.151	.885
	Only left	29	30.3	5.06	.673	.526	28.4	4.20	-.360	.731
	Only right	29	30.4	3.55	1.06	.328	29.6	7.00	.216	.836
TTR lexical verbs	Bilateral off	.63	.730	.071	3.73	.010*	.713	.070	3.12	.020*
	Bilateral on	.63	.676	.063	1.91	.105	.683	.082	1.71	.137
	Only left	.63	.693	.110	1.51	.182	.659	.130	.582	.582
	Only right	.63	.690	.160	.990	.361	.677	.116	1.08	.324
Number of copula and modal verbs	Bilateral off	12	17.4	3.99	3.60	.011*	14.3	6.82	.886	.410
	Bilateral on	12	15.9	5.18	1.97	.096	14.4	5.53	1.16	.290
	Only left	12	19.0	4.36	4.25	.005*	15.0	4.24	1.87	.111
	Only right	12	13.4	5.71	.662	.533	14.1	3.98	1.43	.204
MLU	Bilateral off	8.63	6.99	1.09	-3.97	.007*	7.35	1.03	-3.31	.016*
	Bilateral on	8.63	8.49	2.02	-.183	.860	6.92	1.34	-3.37	.015*
	Only left	8.63	7.87	.576	-3.51	.013*	7.74	1.20	-1.96	.098
	Only right	8.63	7.73	2.47	-.96	.375	6.58	1.44	-3.78	.009*
% correct sentences	Bilateral off	.93	.731	.098	-5.37	.000*	.676	.155	-4.34	.005*
	Bilateral on	.93	.723	.057	-9.55	.002*	.770	.080	-5.32	.002*
	Only left	.93	.703	.091	-6.61	.001*	.736	.165	-3.11	.021*
	Only right	.93	.743	.128	-3.87	.008*	.711	.159	-3.64	.011*
Finiteness index	Bilateral off	.99	.967	.019	-3.20	.019*	.946	.026	-4.44	.004*
	Bilateral on	.99	.941	.036	-3.55	.012*	.971	.031	-1.60	.162
	Only left	.99	.950	.033	-3.24	.018*	.950	.034	-3.14	.020*
	Only right	.99	.967	.038	-1.58	.164	.963	.043	-1.65	.150

Legend: PD-left = patients with predominant dopamine depletion of the left hemisphere; PD-right = patients with predominant dopamine depletion of the right hemisphere; TTR = type token ratio; % correct sentences = percentage of correct sentences; MLU = mean length of utterance; Stand. Dev = standard deviation.* $p < 0.05$.

was stimulated. For PD-right, the finiteness index was within normal range in the condition bilateral stimulation off and only stimulation of the left STN.

The mixed repeated measures ANOVA with bilateral stimulation (on versus off) as within-subject variable and asymmetric dopamine depletion as between-subject factor revealed no main effects for stimulation nor asymmetric dopamine depletion. However, there were significant interaction effects between bilateral stimulation (on versus off) and the lateralization of dopamine depletion for three linguistic parameters: number of nouns (F (1,12) = 6.086, *p* = .030), MLU (F (1,12) = 4.858, *p* = .048) and finiteness index (F (1,12) = 5.355, *p* = .038). Further pairwise Bonferroni corrected post-hoc analysis revealed that bilateral stimulation yielded a significantly increase in both the number of nouns (p = .045) and MLU (*p* = .032) for PD-left, compared to no stimulation. For PD-left, there was no significant difference between bilateral stimulation on and off for the finiteness index. The Bonferroni corrected post-hoc tests demonstrated no significant difference between bilateral stimulation on and off for PD-right in the number of nouns, MLU, and the finiteness index.

The mixed repeated measures ANOVA with left STN stimulation only versus right STN stimulation only as within-subject variable and asymmetric dopamine depletion as between-subjects factor, showed a significant main effect for stimulation in the number of copula and modal verbs (F (1,12) = 5.283, *p* = .040). There were no significant main effects for asymmetric dopamine depletion. No significant interaction effects could be reported between stimulation of the left STN only and stimulation of the right STN only with the lateralization of dopamine depletion on the linguistic parameters. The additional comparison of both stimulation conditions for both PD groups separately, indicated for PD-left a borderline significant difference between left STN stimulation only and right STN stimulation only (*p* = .061). No significant differences were found between stimulation conditions for PD-right. The results for the parameters number of nouns, number of copula and modal verbs, MLU and finiteness index are, for both groups, visualized in Figure 6.1.

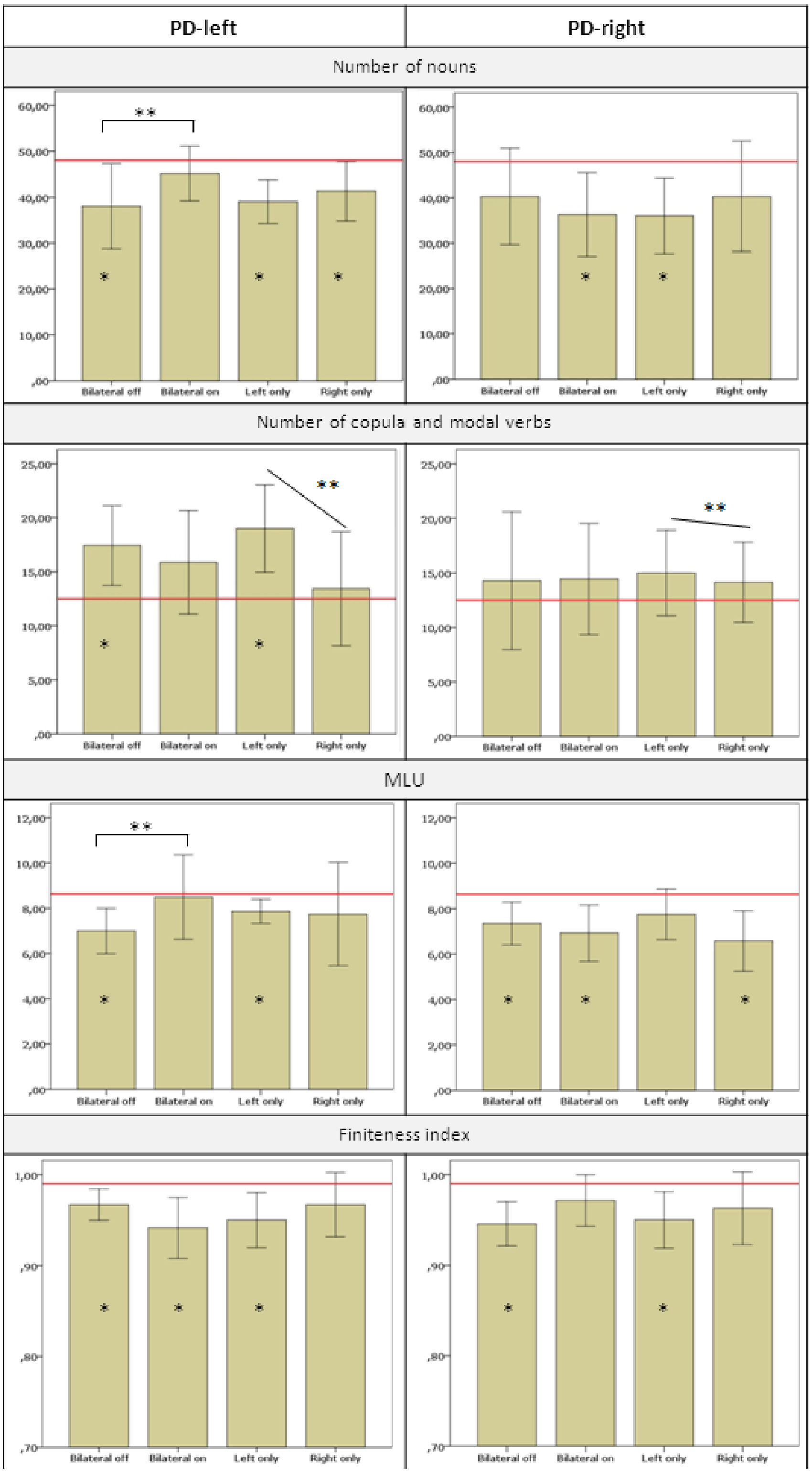

Fig.6.1 Comparison of the mean score with 95% confidence intervals of each PD group separately for the parameters number of nouns, number of copular and modals verbs, mean length of utterance (MLU), and finiteness index with the norm scores. The horizontal line represents the norm mean for each parameter. X-axis represents the four stimulation conditions, bilateral STN stimulation off (bilateral off), bilateral STN stimulation on (bilateral on), left STN stimulation only (left only), right STN stimulation only (right only).

*significant deviation from norm mean $p < .05$; ** main stimulation effect $p < .05$.

Discussion

The current study aimed to investigate the interaction between asymmetry of dopamine depletion with alterations of spontaneous language production. Secondly, the influence of different conditions of STN stimulation on spontaneous language production was examined.

Linguistic difference depending on asymmetric dopamine depletion

The laterality of motor symptoms is associated with spontaneous language production. In the direct comparison of both PD-groups, the PD-right group had a lower finiteness index, indicating more mistakes in verb inflection than the PD-left group. Verb inflection deficits in PD have been described before (Colman et al., 2009; Longworth, Keenan, Barker, Marslen-Wilson, & Tyler, 2005; Ullman et al., 1997), but never in relationship with dopamine depletion asymmetry. Colman et al. (2009) suggested that executive dysfunctions underlie verb inflection problems. However, no compelling evidences have been found for different performances between PD-right and PD-left in executive functioning (Verreyt et al., 2011). In this study, the interference of executive functioning cannot be refuted nor confirmed, due to a lack of specific objective data on this topic for our subjects. Another possibility is that the low finiteness index in PD-right results from the deterioration of the left hemispheric syntactic language functions. Because of the extent of the disease, although dopamine depletion was still asymmetric, all subjects already showed bilateral deterioration of the nigrostriatal system. When comparing both PD groups with the normative data, there were some indications that low finiteness index originated from left hemispheric syntactic language dysfunctions. First, there was a significant decrease of the finiteness index in both PD groups, indicating that both groups encounter difficulties with verb inflection compared to healthy subjects. In addition, there were a reduced number of nouns and an increased number of copula and modal verbs in PD-left compared to the normative data, which were not present in the comparison between PD-right and the normative data. The reduced number of nouns found for the PD-left group can be explained in terms of their grammatical function (Grossman et al., 2003; Peran et al., 2003). Nouns obtain a thematic role in a grammatical structure and can be partially replaced by function words (e.g. pronouns), in contrast with verbs, which have a dominant role in sentence generation, as an assigner of thematic roles (Altmann & Troche, 2011). The increased use of copula and modal verbs can be interpreted as a compensatory mechanism to overcome morphosyntactic difficulties by postponing the mapping of open class words onto the grammatical structure (Hinaut & Dominey, 2013) or by avoiding inflection of lexical verbs. Although these findings come from an indirect comparison of both PD groups via normative data, it appears that only PD-left patients have an excessive use of copula and modal verbs and a reduced number of nouns. So perhaps these deviations are a compensatory strategy, which is not present in PD-right patients. Unfortunately, because of the lack of functional imaging data in this study, all assumptions on neural reorganization are speculative. A longitudinal study on the evolution of spontaneous language and the possible compensatory mechanism introduced during the different stages of the disease using functional imaging would be valuable to investigate this more fundamentally.

It must be mentioned that these results cannot be blindly transposed to PD patients without DBS in off-medication condition. Firstly, all these patients maintained their optimal doses of medication during testing. It has been reported that medication improves linguistic functions (De Letter, Van Borsel, & Santens, 2012), so our results are probably better than without medication. Although an off-medication investigation would be preferable, it would induce effects of strains due to off-symptoms, which are eventually unsupportable for some patients. Furthermore, by maintaining the medication state the same in the four conditions, we tested only the effect of stimulation, not of medication. Secondly, no information is available at the moment on long-term effect of DBS stimulation on language and how it differs from non-STN-DBS implanted patients. Finally, microlesioning caused by STN surgery and the presence of electrodes might influence the language outcome, but again no data on this subject is available at the moment.

Effects of STN stimulation depending on asymmetric dopamine depletion

Asymmetric dopaminergic depletion influences the effect of STN stimulation. These interactions are only detectable for PD-left in two conditions: with and without bilateral stimulation. PD-left patients have an increased MLU and number of nouns when stimulation is bilaterally on, compared to bilateral stimulation off. These interaction effects support the hypothesis of our previous study (Batens et al., 2014), that if you do not take asymmetric dopaminergic depletion into account the effects of STN stimulation on spontaneous language production are averaged out. However, it is likely that there are more variables interacting with the effect of STN stimulation, as the mean scores of the linguistic parameters of both PD-groups with the normative data clearly deviate differently from normative data, while they are not statistically detectable in direct comparisons. The same applies to the lateralized effect of STN stimulation (stimulation of the left STN only versus stimulation of the right STN only). There was one main effect detectable for the number of copula and modal verbs. Stimulation of the left STN only resulted in an excessive number of copula and modal verbs compared to stimulation of the right STN only. Although further statistically analysis did not reveal an interactions effect with asymmetric dopamine depletion, the differences between both PD-groups were clearly visible. The PD-left group had a larger number of copula and modal verbs than the PD-right group when only the left STN was stimulated. The additional statistical analysis revealed that with stimulation of the right STN only, the number of copula and modal verbs decreased noticeably for the PD-left group, while for the PD-right group this decrease was not as visible. So perhaps this main effect was rather an interaction effect that was not statistically measurable due to interference of other variables. Stimulation parameters are one of the variables that are known to influence the outcome of DBS. Stimulation parameters that are beneficial for motor function, which are of primary interest for the treating physicians, do not necessarily correspond to the optimal parameters for cognitive function or speech (Hershey et al., 2008; Tripoliti et al., 2008). Another consideration is that the localization of the electrode within the STN, with a resulting effect on different somatotopically arranged areas within the motor part of the STN, can influence the results (Tripoliti et al., 2008).

The PD-left group seems to benefit from STN stimulation for three linguistic parameters: number of nouns, MLU, and number of copula and modal verbs. Bilateral stimulation normalizes the number of nouns, and MLU. Stimulation of the right STN only normalizes the number of copula modal verbs (see discussion above). No linguistic changes were detectable when only the left STN was stimulated. These results suggest that for PD-left patients stimulation of the least dysfunctional nigrostriatal network is necessary to normalize spontaneous language production and contrast with the idea that STN stimulation has a negative effect on hemisphere specific language functions (Schulz et al., 2012).

For some linguistic parameters (percent of correct sentences and variation of lexical verbs) there seems to be no interaction between asymmetric dopamine depletion and STN stimulation. For the percentage of correct sentences, no differences are noticeable over the various stimulation conditions. It is possible that the percentage of correct sentences is not sensitive enough to detect minor changes in language production by STN stimulation. The variation of lexical verbs normalizes with STN stimulation, regardless of PD lateralization or stimulation condition. Perhaps, the increased variation of lexical verbs is due to a more general cognitive deficit present in PD patients, selection, and inhibition of competing alternatives. Because verbs have more lexical alternatives than nouns, they are probably more vulnerable to inhibitory disturbances (Peran et al., 2003). The suppression and selection of irrelevant and relevant alternatives demands balanced levels of dopamine, not only in the striatum but also in the prefrontal cortex. Imbalance within cortico-basal ganglia-thalamocortical circuits can lead to a disturbance of competition and inhibition (Crescentini et al., 2008; Fallon, Williams-Gray, Barker, Owen, & Hampshire, 2013; Silveri et al., 2012), causing increased competition among lexical verbs in PD. STN stimulation probably restores the imbalance between competition and inhibition within the cortico-basal ganglia-thalamocortical circuits (Crescentini et al., 2008; Fallon, Williams-Gray, Barker, Owen, & Hampshire, 2013), regardless of which STN side is stimulated.

Although this study has limitations, (e.g. small sample size, tested while on anti-Parkinson medication) it encourages including asymmetric dopamine depletion as an influential variable in further linguistic PD studies. Larger study groups are necessary to unravel all variables that influence the spontaneous language production in PD. Finally, a better understanding of DBS effects and organization of language may contribute to more refined DBS settings and a better overall outcome.

Conclusion

Asymmetric dopamine depletion was one of the factors that interacted with the effect of STN stimulation on spontaneous language production. The spontaneous language production of PD patients differed depending on the hemisphere with the largest dopamine depletion. PD-right patients made proportionately more verb inflection errors than PD-left patients did. Only for PD-left patients, sentence production improved significantly by bilateral stimulation. Finally, even when asymmetric dopamine depletion was taken into account, the effect of STN stimulation varied depending on the linguistic parameters.

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The influence of subthalamic nucleus stimulation on pragmatic language production in Parkinson's disease

CHAPTER 7

Van Lier, S., Batens, K., Van Roost, D., Santens, P., Van Herreweghe, M. & De Letter, M., (accepted). The influence of subthalamic nucleus stimulation on pragmatic language production in Parkinson's disease. *Acta Neurologica Belgica*.

Abstract

Introduction: While the influence of deep brain stimulation (DBS) of the subthalamic nucleus (STN) on the comprehension of pragmatic language in Parkinson's disease has been the focus of studies, its impact on production, however, has yet to be elucidated.

Aim: Investigating the influence of DBS-STN on pragmatic language production in spontaneous speech by comparing different stimulation conditions (1) and evaluating the effect of asymmetric dopaminergic denervation (2).

Method: This paper included 18 patients with advanced idiopathic PD with STN-DBS. (Ten PD patients with predominantly left hemispheric dopamine denervation (PD-left) and eight PD patients with predominantly right hemispheric dopamine denervation (PD-right)). The pragmatic components 'communicative functions' and 'conversational skills' were evaluated by analysing the spontaneous language production in four stimulation conditions.

Results: STN stimulation did not appear to influence the pragmatic production skills. Only when asymmetric dopamine depletion was taken into account the parameter 'Giving an explanation' interaction was detectable.

Conclusion: STN-DBS appears to have some influence on the production of pragmatic language depending on asymmetric dopaminergic denervation. Suggestions are made for further research of pragmatic production in Parkinson's disease.

Keywords

Parkinson's disease, subthalamic nucleus stimulation, pragmatic language production, asymmetric dopaminergic depletion.

Introduction

Parkinson's disease (PD) is the second most frequent neurodegenerative disorder with a prevalence of approximately 4 to 6 million people worldwide (Bartels & Leenders, 2009). The disease is mainly characterized by a loss of dopaminergic neurons in the substantia nigra, which ultimately results in a dysfunction of the cortico-basal ganglia-thalamocortical circuits (Bartels, 2009). PD is associated with motor symptoms such as akinesia or bradykinesia, resting tremor, rigidity, and postural instability (Jankovic, 2008), which results in gait, speech and swallowing problems. A hallmark of PD is the asymmetry of motor symptoms, which reflects the asymmetric degeneration of dopaminergic neurons (Djaldetti, Ziv, & Melamed, 2006; Kempster, Gibb, Stern, & Lees, 1989). This lateralized predominance of symptoms remains noticeable throughout the course of the disease, even long after the disease becomes clinically bilateral (Antonini et al., 1995; Cronin-Golomb, 2010; Djaldetti et al., 2006). Asymmetric degeneration of dopaminergic neurons also affects non-motor and cognitive functions (Cubo, Martinez Martín, Martin-Gonzalez, Rodríguez-Blázquez, & Kulisevsky, 2010; Kempster et al., 1989; Riederer & Sian-Hülsmann, 2012; Verreyt, Nys, Santens, & Vingerhoets, 2011), as such difficulties with orientation, mental imagery, and visuospatial attention are observed in PD patients with more severe right-hemispheric dopamine depletion. On the other hand, problems in verbal memory are more commonly associated with more profound nigrostriatal degeneration in the left hemisphere. Studies examining executive functions lead to an inconclusive answer with respect to asymmetry (Verreyt et al., 2011).

PD patients often experience cognitive, social, and linguistic problems, which impair their communicative skills (Holtgraves, Fogle, & Marsh, 2013). The effectiveness of speech and language outcome is strongly influenced by the pragmatic abilities of the speaker. Pragmatics has been defined as the use of language within the social and situational contexts (Geurts & Embrechts, 2010; Martin & McDonald, 2003). The context determines the type and form of communicative intentions, the information that is given, and the manner conversations are organized (Roth & Spekman, 1984). Based on this vision, Roth and Spekman (1984) made a pragmatic model where context is central and is connected with three central pragmatic components (communicative functions, presupposition, and conversation organization), encompassing a broad array of skills, which all interact mutually.

The communicative functions component contains all skills necessary to transfer the intentions of a speaker (e.g. giving/requesting information, negation, giving/requesting explanation, etc.). The presupposition component includes the ability to process implicit information, i.e. 'the shared background knowledge, which the speaker and hearer assume to be true (Eisele, Lust, & Aram, 1998).' Finally, the conversation organization components are all skills necessary to initiate, conduct, repair, and end a conversation.

The pragmatic production skills of people with PD reveal difficulties on every pragmatic component: communicative functions (e.g. the use of gestures and mimics, and their utterances are less informative than those of control subjects), presupposition (deficits in conciseness and feedback) and conversation organization (misplaced pauses) (Holtgraves et al., 2013; McNamara & Durso, 2003).

Before elaborating more in depth, a brief explanation for the neural substrates, which underlie the organization of pragmatic language, is required (Bordini, Garg, Gallagher, Bell, & Garell, 2007). While the left hemisphere is dominant when it comes to language processes, it has been demonstrated that the right hemisphere too takes part in certain modalities (Lindell, 2006), such as the processing of 'narrative and discourse-level material,' which includes metaphorical language use, narratives and conversations (Kuperberg et al., 2000). All of these are important elements of pragmatic language use. However, the neurophysiological organization of pragmatic language is highly complex, as it comprises a vast set of different neural substrates. More specifically, according to Kuperberg et al. (2000), especially the right-superior and middle-temporal gyri are active during the aforementioned processes. Yet, other studies found that the right hemispheric (dorsolateral) frontal lobe is important for the comprehension of certain pragmatic abilities (Alexander, Benson, & Stuss, 1989; Stowe, Haverkort, & Zwarts, 2005). Alexander et al. (1989), assumed that damage to the entire right medial area results in high-level language deficiencies. They argue that damage to the lateral parietal and temporal association cortical area - which are involved in cognitive processes - results in 'a complex disturbance in inferential reasoning, in communicating implicit affective intentions, and in maintaining a coherent, direct point in narratives (Alexander et al., 1989).' A recent functional neuroimaging study, which compared the neural activation in narrative production and narrative comprehension, confirmed the involvement of the aforementioned areas (AbdulSabur et al., 2014). However, clear lateralization differences were described between production and comprehension. Narrative production seems to engage more left hemispheric regions, including premotor and prefrontal regions, as well as the basal ganglia and thalamus, whereas narrative comprehension elicited a bilateral activation.

For this study, patients with advanced PD were included, in whom DBS STN was considered the best therapeutic option. This creates the opportunity to assess the effects of STN stimulation on pragmatic language production in people with PD. Only recently, the first study on the effects of STN stimulation on pragmatic comprehension was published, which did not observe any impact of STN stimulation on the comprehension of metaphors (Tremblay et al., 2015). Other pragmatic comprehension difficulties, like impairments in interpreting figurative language (Lewis, Lapointe, Murdoch, & Chenery, 1998), irony (Monetta, Grindrod, & Pell, 2009), humour (Berg, Björnram, Hartelius, Laakso, & Johnels, 2003), the comprehension of a speech act (the specific intention a person anticipates to convey with an utterance) (Holtgraves, McNamara, Cappaert, & Durso, 2010), and inference (McKinlay, Dalrymple-Alford, Grace, & Roger, 2009), have not been examined in view of STN stimulation effects. To our knowledge, there have not been any studies so far which addressed the effect STN stimulation of pragmatic language production in spontaneous speech.

The aim of this study was to answer following specific research questions:

1. Do pragmatic aspects of spontaneous language production in PD differ depending on the stimulation conditions?
2. Does STN stimulation interact with the side of predominant dopamine depletion, influencing pragmatic aspects of spontaneous language production in PD?

Methods

Patients

Eighteen participants in the advanced stage of idiopathic PD (following the definition of Gelb, Oliver, and Gilman (1999)) were included by means of convenience sampling in this single-centre study. They were all considered appropriate candidates for STN stimulation because of severe and fluctuating symptoms that affected the quality of life. Before surgery, all subjects underwent intensive neurological and neuropsychological testing. Clinical assessment and magnetic resonance imaging indicated that there were no co-morbid neurological diseases. The patients were all native Dutch speakers, who reported no premorbid language disorders, vision or hearing problems. Their handedness was determined by the Dutch Handedness Inventory (Van Strien, 1992) for which scores may range from -10 for extreme left-handedness until +10 for extreme right-handedness. The test indicated that thirteen patients were completely right handed (+10), two strongly right handed (+9), one moderately left handed (-6) and two ambidextrous (-1 and -3). The hemispheric language predominance was defined by means of a dichotic listening task (Kimura, 1961) and indicated that the left hemisphere was the language dominant hemisphere for all included patients. Neuropsychological assessment revealed no signs of dementia or major depression. None of the patients had a history of psychiatric disorders or substance abuse.

The lateralization of motor symptoms was determined for all subjects by the motor scores of the Unified Parkinson´s disease Rating Scale, the clinical evaluation of the neurologist, and the patient's subjective feelings of motor asymmetry. Eight patients had primarily left-sided motor disturbances reflecting predominant right hemispheric dopamine depletion (PD-right). The other ten PD patients had primarily right-sided motor disturbances with predominant left hemispheric dopamine depletion (PD-left).

To ensure that nobody had developed dementia since DBS surgery, all patients were screened using the Montreal Cognitive Assessment (MOCA) (Dalrymple-Alford et al., 2010) before inclusion in this study. The clinical and demographic features are further described in Table 7.1. The stimulation parameters of each subject are summarized in Table 7.2.

Neurosurgery

The neurosurgical placement of electrodes in the STN was done using a conventional stereotactic technique with indirect targeting, combining atlas coordinates, micro-electrode recording, and intra-operative macro-electrode stimulation to determine optimal location of stimulation contacts. Quadripolar electrodes (Medtronic 3389, Medtronic, Minneapolis) were implanted and external stimulation was done for at least one week before implantation of and connection to the pulse generator in the abdominal wall.

Table 7.1 Medical and demographic features of PD patients (adapted).

	Patient	Age (years)	Hand preference [a]	PD duration (years)	DBS duration (months)	NSVO-Z (%) [b]	MOCA [c]
Right-sided motor symptoms predominance	1	66	10	13	6	95*	23
	2	58	10	10	37	99	21
	3	71	10	19	35	100	27
	4	56	10	16	12	98	25
	5	57	10	16	93	83*	27
	6	54	10	10	20	98	21
	7	71	10	15	40	96	23
	8	45	10	12	3	97	27
	9	61	10	11	3	98	27
	10	68	9	9	3	98	25
GA SD		60.70 8.35		13.10 3.28	24.6 28.09		24.60 2.46
Left-sided motor symptoms predominance	11	47	10	12	3	98	25
	12	57	-1	14	7	98	25
	13	41	-6	13	106	86*	23
	14	57	10	14	65	83*	22
	15	60	-3	14	36	90*	26
	16	73	9	15	87	98	21
	17	53	10	16	80	87*	28
	18	65	10	7	3	100	28
GA SD		56.63 10.00		13.13 2.75	48.38 41.53		24.75 2.60
Total GA SD		58.89 9.08		13.11 2.97	35.50 35.61		24,67 2.45

Legend: [a] Hand preference is measured with the Dutch Handedness inventory, scores may range from -10 for extreme left-handedness until +10 for extreme right-handedness (Cronin-Golomb, 2010); [b] NSVO-Z = the Dutch Intelligibility Assessment at sentence level in bilateral stimulation on condition (Martens et al., 2010); *a score lower than 96% is considered to be dysarthric for people under the age of 70; [c] MOCA = Montreal Cognitive Assessment (Dalrymple-Alford et al., 2010); GA = group average; SD= standard deviation.

Table 7.2 Summary of the individual stimulation parameters (adapted).

Patient	Left stimulator				Right stimulator			
PD-left	Pole	Amplitude	Pulse width	Frequency	Pole	Amplitude	Pulse width	Frequency
1	1-case+	1,8	90	130	9-case+	2,2	90	130
2	1-2+	4,5	90	130	9-case+	4	90	130
3	3-case+	3,7	90	130	10+11-	2,5	60	130
4	2-3-	2,5	90	130	9-10-11+	2,7	90	130
5	1-2+	5,3	90	130	9-10-11+	5	90	130
6	2-3-case+	1,8	90	130	8+9-10-11+	3	90	130
7	0+1-2-3+	3,1	60	130	10-case+	3,1	60	130
8	1-	3,7	90	130	9+,10-,11-	4	90	130
9	1-	2,5	90	130	10-	2,0	90	130
10	1-	1,5	90	130	9-	1,0	90	130
GA SD		3.04 1.25	87 9.49			2.95 1.15	84 12.65	
PD-right	Pole	Amplitude	Pulse width	Frequency	Pole	Amplitude	Pulse width	Frequency
11	0-1-	2,2	90	130	10-11-	2,6	90	130
12	1-case+	3	90	130	9-case+	3	60	130
13	1-2-	2	90	130	10-case+	1,1	60	130
14	3+2-	4	90	130	9-11+	4,3	90	130
15	1-case+	2,3	90	130	9-10-	2,3	90	130
16	1-2-	2,9	60	130	10-case+	3,3	60	130
17	2-case+	3,5	60	160	11-case+	2	60	160
18	1-,2+	2,3	60	130	9-,10-	2,3	90	130
GA SD		2.78 0.70	78.75 15.53			2.61 0.95	75 16.04	
Total GA SD		2,92 1.03	83.33 12.83			2.80 1.05	80 14.55	

Legend: GA = group average; SD= standard deviation; PD-left = PD patients with predominant left hemispheric dopamine depletion; PD-right= PD patients with predominant right hemispheric dopamine depletion.

Neurolinguistic analysis

In order to verify that speech intelligibility was not an interfering factor for reliable assessment of the pragmatic language production, the speech intelligibility of all subjects was judged in every stimulation condition using the "Nederlandstalig spraakverstaanbaarheidsonderzoek zinsniveau" (NSVO-Z), "Dutch Intelligibility Assessment at sentence level" (DIA-S) (Martens, Van Nuffelen, Van den Putte, Wuyts, & De Bodt, 2010). NSVO-Z is a computer program that randomly selects 18 nonsense sentences from a database containing 1200 sentences, blinded from the test evaluator. The subject was asked to read the sentences aloud while being recorded. Next, all sentences were transcribed and compared to the target sentences. The intelligibility score was calculated as the percentage of correctly identified words. For people under the age of 70, a score lower than 96% is considered to be indicative of impaired speech intelligibility. Above the age of 70, a score below 93.1% is interpreted as impaired speech intelligibility. Based on the NSVO-Z results, two out of ten PD-left patients and four out of eight PD-right patients were labelled having impaired speech intelligibility. As the speech intelligibility scores of every patient were comparable in every stimulation conditions only the speech intelligibility scores in stimulation ON were represented in Table 1 to avoid repetition and increase clarity.

First, to evaluate the pragmatic language production in spontaneous language production, the pragmatic functions were delineated as described in the model of Roth and Spekman (1984): communicative functions, presupposition, and organization of the conversation. Subsequently the existing standardized observation scale and pragmatic test were checked to see if they meet the requirements to examine these pragmatic functions. The *Nijmeegse Pragmatiektest (NPT)* designed by Embrechts, Mugge, and Van Bon (2005) is a standardized Dutch test that evaluates the pragmatic skills of children. Within this test thirty-one pragmatic skills are being assessed, which are deviated into three categories. Two out of three test categories are based on the model of Roth and Spekman (1984) and evaluate the spontaneous language production. The third category judges the ability to retell a story. Because we are interested to evaluate the pragmatic dysfunctions in spontaneous language production in PD patients, the first two categories best target these requirements. The first category is "communicative functions" which contains skills such as requesting information, an explanation, a certain action, or a clarification, giving a suggestion, information, an explanation or an instruction, talking about other people's activities, negotiating and enquiring the wish of somebody. The second category is that of "conversational skills" (combination of presupposition and organization of conversation) which entails adjusting your information to the listener's needs, talking about something beyond the present moment, repeating something when it is unclear for the listener, taking the prior knowledge of your listener into account, grabbing the attention of somebody, opening and closing a conversation, and turn-taking.

Spontaneous language samples were recorded by means of a semi-standardized interview without time constraints in order to verify the status of the skills of both categories (author KB). During these examinations, the subjects were asked to answer open-ended autobiographical questions, which referred to topics such as work, family and housing, travelling, leisure and general interests. Afterwards the first three hundred words of every language samples were judged by one experienced linguist (author SVL), who had not conducted the interviews and was blinded from patients' dopamine depletion asymmetry and the STN stimulation conditions. The patients were assessed in four STN stimulation conditions: bilateral stimulation ON, bilateral stimulation OFF, stimulation of the left STN only and stimulation of the right STN only. To avoid order or sequence effects within subjects, conditions were randomized. Furthermore, the patients maintained their optimal doses of medication during the testing, which was conducted on one day. After switching to a new stimulation condition, there was at least a fifteen-minute break to reassure that the patient was adapted to the new STN stimulation condition. The audio samples were recorded digitally on a notebook (Dell Laltitude E 6500) using a condenser stereo microphone (Sony ECM-MS907) and the acoustic software Praat (Boersma, 2002) in a quiet room without distractions.

Statistical analysis

All statistical analyses were performed in IBM SPSS Statistics 22 for Windows. The scores of each pragmatic variable were compared in the four stimulation conditions using the non-parametric test for paired measures (Friedman test). Post hoc analyses were done using the Wilcoxon signed rank test. Subsequently, each pragmatic skill in the four stimulation conditions was compared separately depending on the lateralization of their motor symptoms also using the non-parametric test for paired measures (Friedman test). Post hoc analyses were again done using the Wilcoxon signed rank test. For the Friedman test, a p-value less than .05 was considered significant. Due to multiple comparisons (n=8), a Bonferroni correction was applied for the Wilcoxon signed rank test, resulting in a significance level of p< .006.

Table 7.3 Comparison of all pragmatic variables in the different stimulation conditions (Friedman).

Communicative functions	**Complete group**	**PD-left**	**PD-right**
Request for an explanation	.084	.248	.392
Request for a clarification	.640	.701	.719
Describing emotions	.440	.818	.178
Giving suggestions	.468	.801	.194
Giving information	1.00	1.00	1.00
Giving instructions	.300	.300	.300
Request information	.392	.572	.468
Request for a certain action	.572	.112	.300
Talking about other people's activities	.340	.092	.156
Enquiring the wish of somebody	.392	1.00	.392
Give an explanation	.076	.023*	.014*
Negotiate	1.00	1.00	1.00
Conversational skills	**Complete group**	**PD-left**	**PD-right**
Repeating (when unclear)	.518	.600	.881
Grabbing the attention of somebody	1.00	1.00	1.00
Reason of value judgment	.330	.526	.492
Meaning of preceding sentences	.367	.348	.525
Taking the foreknowledge into account	.641	.392	.370
Talking outside of the conversation	.392	1.00	.368
Turn-taking	1.00	1.00	1.00
Opening a conversation	1.00	1.00	1.00
Closing a conversation	1.00	1.00	1.00

Legend: PD-left = PD patients with predominant left hemispheric dopamine depletion; PD-right= PD patients with predominant right hemispheric dopamine depletion; * $p < .05$.

Results

In the comparison of the four stimulation conditions for the complete group, none of the pragmatic parameters differed significantly. When taking the asymmetric dopamine depletion into account and dividing the groups by their lateralized motor symptoms, the parameter "give an explanation" differs significantly between the four stimulation conditions for both PD-left (p=0.023) and PD-right patients (p=0.014). However, pairwise comparisons between the stimulation conditions reached no significance in the post hoc analyses for both PD-right and PD-left patients. The results of the general comparison of the stimulation conditions with the pragmatic parameters for the complete group and for both PD-left and PD-right groups' separately, are summarized in Table 7.3, whereas the pairwise post-hoc analysis are summarized in Table 7.4. The results for the parameters "give an explanation" are visualized in Figure 7.1 for both PD groups in every stimulation condition.

Table 7.4 Post-hoc comparison of the variable 'giving an explanation' (Wilcoxon signed rank test)

Communicative function: Giving an explanation		
	PD-left	PD-right
Left on vs Right on	.107	.058
Left on vs Bilateral on	.053	.020
Left on vs Bilateral off	.014	.034
Right on vs Bilateral on	.655	.655
Right on vs Bilateral off	.257	1.00
Bilateral off vs Bilateral on	.414	.564

Legend: PD-left= patient with predominantly left hemispheric dopamine depletion; PD-right= patient with predominantly right hemispheric dopamine depletion.

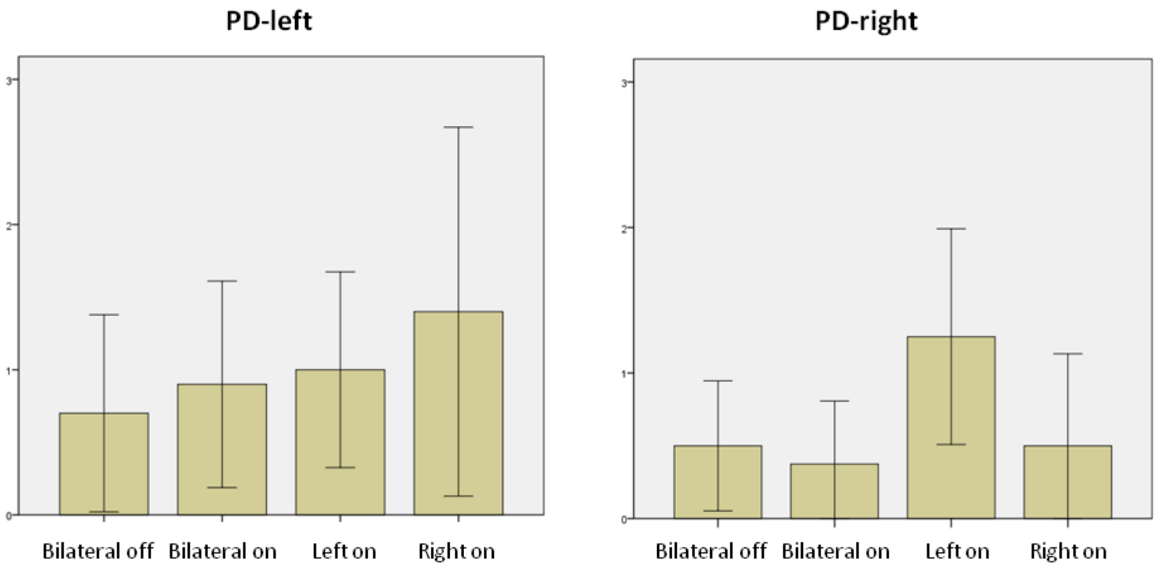

Figure 7.1 Comparison of the mean score with 95% confidence intervals of each PD-group separately for the parameter give an explanation X-axis represents the four stimulation conditions, bilateral STN stimulation off (bilateral off), bilateral STN stimulation on (bilateral on), left STN stimulation only (left only), right STN stimulation only (right only).

Discussion

The current study aimed to investigate the effect of STN stimulation on pragmatic production. Overall, STN stimulation did not appear to influence the pragmatic production skills. Although this is currently the first study which focuses on the influence of STN stimulation on pragmatic language production, the results are in line with the only study on pragmatic comprehension, which also could not observe effects of STN stimulation (Tremblay et al., 2015). The absence of significant stimulation effects does not rule out the potential interaction of DBS STN with pragmatic functions, but might emphasizes the complex, at present poorly understood interaction.

PD-patients form a heterogenic group with heterogenic responses to STN stimulation in cognitive and linguistic processes, as there are multiple potential variables interacting with the outcome (Batens et al., 2014; Yágüez et al., 2014). Asymmetric dopamine depletion is one of the variables that is argued to influence the effect of STN stimulation on language production and the pragmatic functions in particular (Batens et al., 2014; Holtgraves et al., 2010). When asymmetric dopamine depletion was taken into account, STN DBS seemed to affect the way PD patients were able to give an explanation. In other words, depending on the STN stimulation condition, the patients' ability to clarify the consequences of an event differed significantly. Although this interaction could not be retained with further post hoc analysis, some differences were visibly noticeable. Stimulation of the left STN only seemed to increase the ability to explain the consequences of an event compared to the other stimulation conditions, especially for PD-right patients. Additionally, it must be said that the average results of the PD-right patients were lower than the results of the PD-left patients: The ability to give an explanation is inherently linked to the speaker's awareness of the interlocutor's need for extra information. So, not only must the speaker be capable of producing an explanation, in addition they have to be able to understand the context and comprehend when their interlocutor is in need of clarification. Moreover, Mitchell and Crow (2005) highlighted 'the importance of full access to right hemisphere language functions to ensure successful social communication.' In other words, according to them, pragmatic language functions are inherently linked to the right hemisphere and any damage or dysfunction would automatically result in pragmatic deficiencies. Furthermore, pragmatic functioning is also inextricably linked to several cognitive functions, of which some are ascribed to the right frontal cortex, such as awareness of others and one's own mental states (Perkins, 2012). This result suggests that for PD-right patients' stimulation of the least dysfunctional nigrostriatal network seems to increase the ability to explain the consequences of an event. The underlying mechanism on this effect remains to be elucidated. Stimulation of the left STN appears to be involved with left (sub)cortical linguistic networks. This is interesting as pragmatic functions are often attributed to right hemispheric areas, however, a recent functional neuroimaging study revealed a mainly left hemispheric activation for pragmatic production in which a clear involvement of the basal ganglia was suggested (AbdulSabur et al., 2014). Therefore, stimulation of the left STN appears to disturb functioning of the left cortico-basal ganglia-thalamocortical circuits, causing significant changes in pragmatic production.

Pragmatics remains a highly complex linguistic component as a result of the interconnectivity of social and cognitive skills, of which the neurophysiological mechanisms are still elusive (McKinlay et al., 2009). Therefore, the knowledge of the neurophysiological processes underlying pragmatic language production has to be further elucidated if we want to be able to disentangle its interaction with PD and specifically with STN stimulation.

Moreover, the evaluation method, which was used in this study, is probably not being the most suitable method; i.e. a behavioural classification was developed to evaluate pragmatic production skills, which did not consider the underlying neurophysiological networks. It is plausible that different pragmatic production skills share partially the same neurophysiological networks, and thus behavioural evaluations might provide insufficient information about what really goes wrong. Hereby, it can be questioned whether the pragmatic functions should be evaluated by analysing the closest natural way of a conversation - ideally a natural conversation between multiple interlocutors - or whether the evaluation should be guided by - still to be obtained - neurophysiological data, which test underlying processes individually.

Conclusion

There is a limited influence of STN stimulation on pragmatic production, which was only observed when the asymmetric dopamine depletion was taken into account. As bilaterally organized neurophysiological processes seemed to be necessary in pragmatic production, asymmetric dopamine depletion might cause different disturbances within specific pragmatic skills. As such, further neurophysiological assessment of the pragmatic production skills is recommended before the complex interplay of pragmatic production skills and the effects of STN stimulation can be meticulously disentangled.

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One-year follow-up of language production after deep brain stimulation in Parkinson's disease

CHAPTER 8

Batens, K., De Letter, M., Miatton, M., Raedt, R., Duyck, W., Santens, P., & Van Roost, D. (under review). One-year follow-up of language production after deep brain stimulation in Parkinson's disease. *Brain and Language.*

Abstract

Background: In patients with advanced Parkinson's disease, long-term improvement of motor features by subthalamic nucleus deep brain stimulation has been thoroughly demonstrated. However, reports of longitudinal effects on linguistic changes are scarce.

Objective/Hypothesis: The evolution of spontaneous language production in patients with Parkinson's disease was prospectively analysed from baseline until one year after deep brain stimulation. Furthermore, the effects of stimulation parameters, medication dosage, intelligibility, mood, and neuropsychological performances on language outcome were examined.

Methods: The morphosyntactic and semantic performance in spontaneous language production of seven patients was evaluated prior to surgery and one, three, six, and twelve months after surgery in four subthalamic nucleus stimulation conditions: bilateral stimulation on, bilateral stimulation off, stimulation of the left subthalamic nucleus only, stimulation of the right subthalamic nucleus only. The medication dose, the total electrical energy delivered by each electrode, and speech intelligibility were measured at every test moment. All patients were neuropsychologically tested prior to surgery and one year after surgery.

Results: The number of produced nouns diminished immediately after deep brain stimulation without improvement in the further course of the year. Only two patients reached their pre-operative level again. These two patients were administered the highest doses of dopaminergic medication after surgery.

Conclusions: Deep brain stimulation seems to influence the already compromised spontaneous language production negatively. The highly variable results on spontaneous language production seem to be dependent on the interaction of dopaminergic medication and subthalamic nucleus stimulation.

Keywords

Parkinson's disease, longitudinal, deep brain stimulation, spontaneous language production, dopaminergic medication.

Introduction

Deep Brain Stimulation (DBS) has become an established therapeutic option for advanced Parkinson´s disease with motor fluctuations that are refractory to medical treatment (Kleiner-Fisman et al., 2006, Klostermann et al., 2012). Although the mechanism of action is still unclear, DBS is presumed to override the oscillatory patterns of the disrupted networks in Parkinson’s disease (Benabid et al., 1996, McIntyre and Hahn, 2010). At present, in most therapeutic centres the subthalamic nucleus (STN) is the target of choice, as high-frequency stimulation in this nucleus improves all cardinal motor symptoms of Parkinson’s disease while it allows a reduction of dopaminergic anti-Parkinson drug treatment (Fasano et al., 2012). Clinical trials studying these motor features have proven the long-term effectiveness of STN-DBS (Fasano et al., 2012). The effect of high-frequency STN stimulation on language functions is not as straightforward as on motor symptoms (Klostermann et al., 2012). A limited number of studies with small cohorts of patients show varying results (Klostermann et al., 2012). The large variability in linguistic outcome seems to be the result of multiple factors, such as asymmetric dopamine depletion (Batens et al., 2015), executive dysfunctions (Colman et al., 2009), and dysarthria (Illes et al., 1988). It is conceivable that other variables that have not been examined in relationship with linguistic outcomes also influence the results.

Little is known about the evolution of the spontaneous language production in patients with Parkinson´s disease in the course of time after STN-DBS surgery. To our knowledge, only one study (Zanini et al., 2003) specifically examined the spontaneous language production of patients with Parkinson´s disease at more than one point of time after STN-DBS surgery. An overall improvement of morphosyntactic and semantic features was found 2-3 weeks after surgery, relative to the pre-operative state, and it was maintained 1 year after surgery. This improvement was ascribed to a recovered functional equilibrium within the basal ganglia and between the basal ganglia and cortex. To increase the knowledge on the longitudinal effect of STN on spontaneous language, we aimed to answer the following two research questions:

1. Is there an evolution in spontaneous language processing in the first year after starting STN-DBS?
2. Are the linguistic (semantic or morphosyntactic) effects of STN-DBS related to asymmetric dopamine depletion, the side of stimulation, stimulation parameters, medication dosage, intelligibility, mood, and neuropsychological performances?

Methods

Patients

Seven participants in an advanced stage of idiopathic Parkinson's disease (according to the definition of Gelb *et al.* (1999)) were consecutively included in this study. The group consisted of two women and five men, who were implanted at a mean age of 60 (±6) years with an average disease duration of 11 (±2) years. They were all considered appropriate candidates for STN stimulation after intensive neurological and neuropsychological testing, because of severe and fluctuating symptoms affecting the quality of life. Clinical assessment and magnetic resonance imaging revealed that there were no co-morbid neurological diseases. None of the patients had a history of psychiatric disorders or substance abuse.

Patients were all native Dutch speakers, who reported no premorbid language disorders, vision or hearing problems. The hemispheric language predominance was defined by means of a dichotic listening task (Kimura, 1961), which showed a left hemispheric language dominance in all subjects. Motor symptom predominance was agreed upon based on the motor scores of the Unified Parkinson´s disease Rating Scale, the clinical evaluation of the neurologist and the patient's subjective feelings of motor asymmetry. Two patients had primarily left-sided motor disturbances reflecting predominant right hemispheric dopamine depletion (PD-right). The other five patients with Parkinson´s disease had primarily right-sided motor disturbances, hence predominant left hemispheric dopamine depletion (PD-left). Handedness was determined by the Dutch Handedness Inventory (Van Strien, 1992), the scores of which range from -10 for extreme left-handedness to +10 for extreme right-handedness. Six patients were completely right-handed (+10 or +9) and one patient was ambidextrous (-1). A detailed description of the medical and demographic features is represented in Table 8.1.

Table 8.1 Medical and demographic features of PD patients.

Patient	Age (years)	Hand preference [a]	Language predominance [b]	Motor symptoms predominance	PD duration (years)
1	65	10	Left	RmPD	12
2	62	10	Left	RmPD	16
3	45	10	Left	RmPD	12
4	61	10	Left	RmPD	11
5	68	9	Left	RmPD	9
6	56	-1	Left	LmPD	13
7	65	10	Left	LmPD	7
GA SD	60,29 7.73				11.43 2.88

Legend:[a] Hand preference is measured with the Dutch Handedness inventory (Van Strien, 1992) [b] Hemispheric language dominance is defined with the dichotic listening task; [c] DIA-S = the Dutch Intelligibility Assessment at sentence level (Martens, H., Van Nuffelen, G. & De Bodt M., 2010;. RmPD = right sided motor predominance; LmPD= left sided motor predominance.

Procedure

Preoperatively, all patients underwent a neurolinguistic and neuropsychological evaluation. The evaluation took place approximately six months before surgery. This time window corresponded to the average time needed to receive approval for reimbursement of the National Institute for Health and Disability Insurance in Belgium and to schedule surgery. The pre-operative neurolinguistic evaluation was conducted, both with and without the patient´s optimal anti-Parkinson medication. For the evaluation without their anti-Parkinson medication, intake was interrupted at least twelve hours before testing. Between the two test moments, an interval of at least twenty-four hours was respected. The neuropsychological evaluation was only conducted when patients were on their anti-Parkinson medication.

Postoperatively, the neurolinguistic evaluation was conducted one, three, six, and twelve months after surgery. The patients were assessed in four STN stimulation conditions: bilateral stimulation on, bilateral stimulation off, stimulation of only the left STN, and stimulation of only the right STN. To avoid order or sequence effects within subjects, the conditions were randomized. The patients maintained their optimal doses of medication during testing. After switching to a new stimulation condition, there was at least a fifteen-minute break to reassure that the patient was adapted to the new STN stimulation condition. The neuropsychological evaluation was repeated one year after surgery in their optimal anti-Parkinson medication condition with bilateral STN stimulation on. The anti-Parkinson medication was calculated in terms of the levodopa-equivalent daily dose (LEDD), expressed in milligrams, and calculated according to the standardized LEDD formulae described by Tomlinson *et al.* (2010). To assess the stimulation parameters of all subjects in every time period, the total electrical energy delivered (TEED) for each electrode side was measured with the formulae as proposed by Koss *et al.* (2005).

Neurosurgery

The neurosurgical placement of the electrodes in the STN was done using a conventional stereotactic technique with indirect targeting, combining atlas coordinates, micro-electrode recording, and intra-operative macro-electrode stimulation to determine the optimal location of the stimulation contacts. Quadripolar electrodes (DBS lead model 3389, Medtronic Inc., Minneapolis) were implanted and external stimulation was applied for at least one week before implantation of the internal pulse generator in the abdominal wall.

Neurolinguistic analysis

The Dutch Intelligibility Assessment at sentence level (DIA-S) (Martens et al., 2010) was applied in all subjects at every test moment in order to verify that speech intelligibility was not an interfering factor for reliable transcriptions of the language samples. DIA-S is a computer program that randomly selects 18 nonsense sentences, blinded for the test evaluator. The subject was asked to read the sentences aloud while being recorded. Then, all sentences were transcribed and compared to the target sentences. The intelligibility score was calculated as the percentage of correctly identified words. People under the age of 70 are labelled dysarthric when the score is lower than 96% (Martens *et al.*, 2010).

The quantitative analysis of spontaneous language production was conducted as described in the Analysis of Spontaneous Speech in Aphasia (ASTA) (Boxum *et al.*, 2010). The language samples were collected out of a semi-standardized interview without time constraints in which subjects had to answer open-ended autobiographical questions. These questions were referring to topics such as work, family and housing, traveling, leisure and general interests. At least three different topics were addressed during one interview. The first 300 words of each interview were orthographically transcribed for analysis. Also the transcription criteria and analysis method were adopted from the ASTA, thus enabling reference to the normative data of the ASTA (van der Scheer *et al.*, 2011).

Semantic analyses were conducted by counting the number of nouns and lexical verbs as well as their variety (type-token ratio). Type-token ratios (TTR) were calculated by dividing the number of different nouns or lexical verbs by the total number of nouns and lexical verbs respectively. Morphosyntactic evaluation was conducted by counting the number of copula and modal verbs, mean length of utterance (MLU), percentage of correct sentences and finiteness index (proportion of correctly inflected verbs to the total number of clauses containing a verb). Because of the high inter-rater reliability of the ASTA (van der Scheer *et al.*, 2011), all transcriptions and analyses were done by one experienced speech pathologist, who was blinded for patients' dopamine depletion asymmetry, anti-Parkinson medication dosage and the STN stimulation condition.

All audio samples were recorded digitally on a notebook (Dell Latitude E 6500) using a condenser stereo microphone (Sony ECM-MS907) and the acoustic software Praat (Boersma, 2002). Recording took place in a quiet room without distractions.

Neuropsychological evaluation

The neuropsychological battery administered included tests for memory, information processing, and executive functioning. The Rey Auditory Verbal Learning Test (RAVLT) total trials (1-5) (RAVLT-total), short-term recall (RAVLT-stm) and long-term (RAVLT-ltm) recall were selected as memory variables. Information processing was tested by means of verbal working memory (backwards digit span from the Wechsler Adult Intelligence Scale (WAIS-III)) and speed of processing (Stroop Color Word Test (SCWT) card 1). Executive functions were assessed with the Controlled Oral Word Association (COWA) for phonological and semantic fluency and SCWT (card III-II) interference score. The selection of the test for neuropsychological battery was based on the study of Williams *et al.* (2011), who examined the cognitive consequences of DBS for a two-year period, and established reliable change indices for the included variables. Mood and wellbeing was assessed with the Beck

Depression Inventory (BDI). Patients were aware of the study aims and agreed by signing an informed consent. This study was approved by the Ethical Committee of Ghent University.

Statistical analysis

The eight linguistic variables at every time point and in every stimulation condition were compared with each other using a linear mixed model, with stimulation conditions and time point as fixed variable. In addition, both preoperative measuring points were included as measuring points without STN stimulation. Post hoc main effects were compared using a Bonferroni correction.

The Z-scores of all linguistic parameters at every evaluation moment and in every stimulation condition were calculated to measure the magnitude of differences between all ASTA variables at the different test moments and the normative data. Z-scores larger than two were classified as significant, as described in the ASTA (Boxum et al., 2010). A language sample was considered to be divergent if at least one parameter was significantly different.

Pre-operative neuropsychological data were compared with the post-operative data by means of reliable change indices. Differences between the pre- and postsurgical results larger than these reliable change indices were considered to be clinically significant (Williams *et al.*, 2011).

Results

The z-scores of all linguistic parameters at every evaluation moment and in every stimulation condition are summarized in Table 8.2.

Longitudinal evolution of spontaneous language production.

Overall progression

The main effect of time for number of nouns yielded an F ratio of $F(1, 125) = 4.613$, $p = .002$, post hoc analysis showed that the number of nouns was significantly higher prior to surgery than at every test point after surgery (at 1 month: $p = .02$; at 3 months $p = .012$; at 6 months

p = .009; at 12 months p < .001). There was no significant main effect for stimulation (F (1,125) = 1.898, p = .133) nor for the interaction between stimulation and time (F (1,125) = 2.429, p = .182). No other linguistic variables varied significantly across the time or stimulation conditions.

Preoperative status

The spontaneous language production differed in 9 out of 14 (64%) preoperative language samples from the normative data, of which five diverging language samples were recorded with medication and four without medication.

Six out of seven patients had at least one parameter that differed significantly from the normative data: Four patients had only significant morphosyntactic deviations, while two patients had both morphosyntactic and semantic significantly deviating parameters compared to normative data. None of the patients had significant deviations in the number of nouns and MLU. For the morphosyntactic parameter, five patients revealed a decreased percentage of correct sentences, two patients had a lower finiteness index, and one patient had an increased number of copula and modal verbs.

Post-operative status

The spontaneous language production differed in 90 out of 111 (81%) of the postoperative language samples from the normative data. Looking at the time post-surgery, there was a decrease in numbers of deviating language samples as times passes. There were 26 out of 27 (96%) deviating language samples 1 month post-surgery, 24 out of 28 (86%) deviating language samples 3 months post-surgery and 20 out of 28 (71%) deviating language samples 6 and 12 months post-surgery.

To which extent language samples diverged from the norm differed from patient to patient. Patient 1 and Patient 4 had the lowest number of deviating language samples (22 out of 28; 79%). Patient 5 and patient 6 each had 25 out of 28 deviating language samples (89%). All other patients (patient 2, 3, and 7) had only one complete language sample within the normative range (96%).

Table 8.2 Standard deviations of all linguistic parameters at every test moment compared to the normative data of the ASTA.

Patient		Pre-operative		1 month post-operatively				3 months post-operatively				6 months post-operatively				12 months post-operatively			
		with	without	off	on	left	right	off	on	left	right	off	on	left	right	off	on	left	right
1	**Amount of nouns**	0,00	-1,52	-2,03	0,00	-1,65	-0,38	0,38	-0,51	-1,65	-2,54	-1,51	-2,08	-0,99	-0,70	-0,25	-0,76	-1,27	-1,02
	TTR nouns	-0,91	0,92	0,27	-1,69	0,50	-0,33	-2,63	-2,63	-0,25	1,25	1,56	-0,37	1,21	2,17	0,28	1,51	-1,28	1,13
	Amount of lexical verbs	-0,72	1,93	0,72	-1,69	0,24	-1,45	-1,93	-0,48	-0,24	0,48	0,38	0,92	-1,46	-0,51	-1,45	0,24	0,24	0,00
	TTR lexical verbs	0,92	-0,08	-0,33	0,88	0,03	2,18	1,18	0,36	-1,18	-1,64	0,88	-0,34	1,66	0,97	1,78	0,03	-0,27	0,54
	Amount of copula and modal verbs	2,65	0,48	1,69	2,17	-0,48	1,93	3,13	0,00	1,20	1,93	0,79	1,21	-0,12	0,18	0,96	1,93	0,96	1,45
	MLU	-0,78	-0,91	-0,73	-0,25	-1,14	-0,90	-0,79	-0,63	-0,71	-0,26	-0,82	-1,12	-1,11	-1,66	-1,73	-1,99	-1,62	-1,66
	% correct sentences	-1,54	-0,18	-1,28	0,06	-2,68	-3,74	-1,33	-3,17	-1,33	-0,67	-2,83	-1,13	-0,76	-1,21	-1,21	-1,61	-0,05	-0,42
	Finiteness index	0,33	0,33	-0,50	0,33	-1,25	-0,50	0,33	-2,05	-0,62	0,33	0,33	0,33	0,33	0,33	0,33	0,33	0,33	0,33
2	**Amount of nouns**	0,38	-0,51	-1,40	-2,16	-0,76	-2,16	-2,28	-1,40	-1,02	-1,52	-1,78	-2,03	-2,16	-0,38	-2,03	-2,41	-1,27	-2,16
	TTR nouns	-0,19	0,44	0,97	0,58	-0,27	-1,84	1,33	-0,04	-0,13	-0,82	-0,68	0,27	0,58	0,22	-0,91	-1,31	0,70	0,18
	Amount of lexical verbs	-0,72	-0,97	0,24	2,66	3,86	0,24	0,00	0,00	-0,97	2,66	-1,21	0,72	3,38	0,24	1,69	2,42	-0,97	-0,24
	TTR lexical verbs	-0,13	1,91	0,33	-0,50	-0,88	0,03	-0,40	0,54	-0,27	-1,18	-0,80	1,09	-0,02	0,03	-1,43	-1,07	0,09	-1,18
	Amount of copula and modal verbs	0,00	0,24	0,48	-0,72	-0,72	0,00	1,20	-0,48	1,93	-0,24	4,10	0,96	0,24	-0,24	-0,96	1,20	2,41	0,00
	MLU	-0,28	-0,70	-1,83	-0,67	-1,07	-1,42	-0,50	-1,14	-0,77	0,54	-1,25	-1,28	-1,21	-0,97	-0,63	-0,66	-0,80	-0,87
	% correct sentences	-4,72	-2,26	-1,55	-3,60	-3,66	-0,82	-3,88	-5,31	-4,23	-3,00	-3,34	-3,53	-2,58	-2,78	-2,26	-3,38	-3,38	-1,09
	Finiteness index	-2,30	-1,69	-0,48	-2,92	0,33	0,33	-1,42	-3,00	-0,52	-0,57	0,33	-1,42	0,33	-3,71	-0,52	0,33	-0,71	0,33
3	**Amount of nouns**	0,38	-1,27	-2,03	-1,02	-1,90	NA	-2,16	-1,65	-1,65	-0,89	-1,02	-1,90	-2,41	-1,90	-2,79	-1,78	-1,90	-1,52
	TTR nouns	0,79	-0,95	1,05	0,50	-0,79	NA	0,18	0,86	-0,57	-0,35	0,19	1,48	0,84	1,86	-0,85	0,43	-0,03	1,26
	Amount of lexical verbs	-0,24	0,97	2,17	-0,72	0,48	NA	0,24	0,48	1,69	0,48	0,24	1,45	1,21	0,48	1,21	-1,69	1,45	-0,97
	TTR lexical verbs	0,77	-1,60	0,73	1,62	-0,74	NA	-0,88	-1,33	0,59	-0,74	0,64	-0,27	0,96	0,43	-1,18	-0,36	-0,01	0,45
	Amount of copula and modal verbs	0,72	-0,24	0,00	0,00	-0,24	NA	0,24	1,20	0,48	-1,45	0,24	-0,96	0,00	1,69	0,24	1,45	1,20	1,69
	MLU	-0,67	-0,35	-0,90	-0,54	0,54	NA	0,09	0,02	-0,60	0,87	-0,63	-0,19	0,23	-0,66	-1,08	-0,25	-0,58	-1,05
	% correct sentences	-0,69	-2,26	-3,46	-3,93	-4,19	NA	-4,01	-4,56	-2,26	-1,21	-4,24	-3,25	-4,58	-2,89	-3,96	-4,56	-4,23	-6,24
	Finiteness index	0,33	-0,38	-1,12	0,33	-2,11	NA	-1,57	0,33	0,33	0,33	0,33	0,33	0,33	0,33	0,33	-3,27	-1,38	-0,62
4	**Amount of nouns**	0,51	1,78	-1,90	-2,28	3,77	1,02	-2,41	1,27	-0,25	-0,38	-1,02	-1,27	1,14	0,63	-2,41	1,02	-0,13	-2,16
	TTR nouns	0,84	-0,43	1,86	1,33	1,25	0,54	1,71	-0,23	-0,80	-0,61	1,13	0,70	-0,29	0,64	1,28	1,88	0,61	0,98
	Amount of lexical verbs	1,21	0,24	1,21	4,11	-0,62	-0,24	1,93	-2,42	5,31	0,24	0,97	1,69	0,72	1,93	1,93	-0,48	0,48	0,48
	TTR lexical verbs	0,96	1,55	-0,65	0,40	0,69	0,12	-1,30	1,45	-0,20	0,33	0,61	0,08	-0,05	-0,32	0,91	-0,34	0,72	1,90
	Amount of copula and modal verbs	-0,24	-0,48	1,20	-1,45	-0,64	0,24	1,20	1,45	-0,24	-0,48	-1,20	1,45	-0,96	-1,45	-0,72	0,00	0,72	0,96
	MLU	-0,79	-0,53	-0,77	-0,21	-0,98	-0,01	0,05	0,25	-1,40	-1,29	0,17	1,01	-0,79	-0,98	1,17	-0,80	-0,66	0,77
	% correct sentences	-0,08	-1,09	-3,12	-3,12	-0,12	-2,37	-3,13	-0,98	-1,21	-1,21	-0,56	-2,68	-0,54	0,33	-0,92	-0,59	-1,86	-1,92
	Finiteness index	0,33	0,33	-0,59	0,33	0,33	0,33	0,33	0,33	-1,00	-0,68	0,33	-1,22	-1,63	0,33	0,33	0,33	-0,68	0,33

		with	without	off	on	left	right	off	on	left	right	off	on	left	right	off	on	left	right
5	**Amount of nouns**	1,90	-0,25	-1,90	-3,17	-1,14	0,51	-0,51	-2,16	-0,38	-0,51	-0,89	0,00	-0,76	-0,25	-4,31	-1,02	-1,65	-0,89
	TTR nouns	0,02	0,01	-1,55	-0,26	-0,21	-1,33	-3,53	-0,63	-0,33	-0,98	-1,57	-1,17	-0,27	-0,26	-0,57	0,19	-1,29	-1,27
	Amount of lexical verbs	0,97	1,21	1,21	1,45	2,17	-1,93	3,86	0,72	-0,48	0,72	2,42	1,21	-0,72	1,21	5,07	1,45	3,14	-1,21
	TTR lexical verbs	-0,49	-0,65	-1,98	-1,83	-0,46	-0,97	-1,28	-1,18	-0,34	-0,61	-1,07	-0,38	-0,48	-1,18	-0,82	-0,01	-1,40	0,33
	Amount of copula and modal verbs	-0,24	0,24	-0,48	1,69	0,24	2,17	0,24	0,00	1,69	0,00	1,69	2,65	1,45	0,00	3,86	1,93	0,96	0,72
	MLU	-0,65	-0,88	-0,54	-1,35	-1,29	-1,98	-0,35	-1,19	-1,62	-0,35	-1,50	-1,18	-1,05	-1,71	-1,05	-0,59	-0,99	-1,26
	% correct sentences	-2,54	-0,08	-2,07	-2,62	-2,09	-0,83	-2,75	-0,64	-3,00	-4,55	-2,02	-0,02	-0,02	0,15	-3,46	-2,34	-2,09	-1,68
	Finiteness index	0,33	-0,59	-0,52	-1,42	0,33	-1,42	0,33	-0,62	0,33	-2,30	0,33	0,33	0,33	-0,57	-1,89	0,33	-0,54	0,33
6	**Amount of nouns**	-0,65	-0,46	0,25	-2,03	0,63	-1,27	-1,52	0,20	-3,30	0,25	-0,63	-1,02	0,76	-2,66	-1,31	-1,40	-1,52	-1,90
	TTR nouns	1,44	3,00	2,18	1,05	0,88	-0,62	0,92	1,65	0,73	-0,75	1,21	-1,06	-0,01	1,61	-0,68	1,65	-0,47	-0,03
	Amount of lexical verbs	-1,18	2,45	-0,24	0,48	-1,45	0,97	-1,69	-2,15	2,42	-0,24	-0,82	0,97	0,48	2,17	1,02	0,48	-0,75	1,69
	TTR lexical verbs	3,36	0,94	1,27	1,02	1,78	2,00	2,12	2,76	1,03	1,74	2,27	0,61	1,02	0,73	1,85	1,60	2,89	0,84
	Amount of copula and modal verbs	0,34	1,51	0,24	2,65	0,72	1,93	1,20	0,66	1,69	-0,48	1,30	-0,72	-0,48	-0,48	0,00	2,17	-0,59	0,48
	MLU	0,84	0,74	-1,28	0,31	0,12	-0,47	0,52	0,81	2,14	1,76	0,98	2,01	0,06	1,45	2,54	-0,60	0,53	-0,67
	% correct sentences	-0,35	-3,38	-0,02	-1,06	-2,48	-1,15	-0,50	-0,42	-1,01	-1,73	-0,07	-3,18	0,16	-1,50	-2,34	-1,61	-1,86	-0,74
	Finiteness index	0,33	-5,22	-1,75	0,33	-0,71	-0,42	-0,68	0,33	0,33	0,33	0,33	-0,78	0,33	0,33	0,33	-0,52	0,33	0,33
7	**Amount of nouns**	-1,90	0,13	-1,90	-1,27	-2,28	0,63	-0,13	-0,89	-1,14	-1,65	-1,14	-2,41	-0,89	-2,03	-1,52	-1,14	-0,51	-1,02
	TTR nouns	0,73	-1,08	-0,03	-0,29	2,17	0,41	-0,72	-0,05	-1,81	0,86	0,76	-0,88	-0,05	0,66	-0,13	0,76	-0,41	-0,75
	Amount of lexical verbs	2,17	1,45	1,45	-0,24	-0,24	0,24	-1,69	-0,24	-1,21	-0,48	-1,69	-0,24	-1,69	-1,69	-0,97	-0,24	0,72	0,48
	TTR lexical verbs	-0,46	-2,09	-0,53	2,39	0,77	0,94	1,71	-0,53	0,71	0,33	0,47	0,12	-0,77	0,88	0,45	-0,86	-1,18	-0,45
	Amount of copula and modal verbs	-0,24	-0,48	0,72	-1,45	2,65	-1,93	2,17	0,96	0,24	0,00	1,93	0,72	0,48	2,41	0,48	0,00	0,24	0,24
	MLU	0,64	-1,20	-0,34	-0,01	-0,70	1,18	-0,23	0,40	0,81	0,44	-0,59	0,00	-0,86	-0,97	-0,11	-0,47	-0,33	-0,65
	% correct sentences	-3,00	-1,68	-5,50	-3,67	-3,46	-4,17	-6,36	-5,01	-7,17	-4,79	-1,86	-3,00	-3,66	-2,07	-5,08	-2,48	-4,39	-3,46
	Finiteness index	0,33	0,33	-0,65	0,33	-2,05	0,33	-0,68	-1,42	0,33	-0,65	0,33	0,33	-0,68	0,33	-0,50	-0,52	-0,52	0,33

Legend: Standard deviations, comparison with ASTA; dotted underline > 2SD lower than mean, double underline > 2SD higher than mean, grey no significant deviations from mean for the complete language sample NA: not applicable; with: with medication; without: without medication; off: bilateral stimulation off; ON: bilateral stimulation on; left: left STN stimulation only; right: right STN stimulation only; MLU: mean length of utterance; TTR: type token ratio.

All parameters included in the ASTA showed significant differences from the normative data after STN surgery, but the extent and the occurrence of these in an individual patient varied largely.

The number of nouns was the most frequent deviating semantic parameter (20%) showing a decrease in all subjects. Subsequently, the number of lexical verbs, TTR nouns and TTR lexical verbs were aberrant from the normative data in 12%, 4%, and 5% of the samples, respectively. The number of lexical verbs was aberrant in 6 out of 7 patients, showing both a decreased and an increased number compared to normative data. TTR nouns increased in three patients and decreased in two patients. Finally, TTR lexical verbs increased in three patients.

The percentage of correct sentences (44%) was the most frequent deviating morphosyntactic parameter showing a decrease in all subjects. Subsequently, the number of copula and modal verbs, finiteness index, and MLU deviated in 8%, 5%, and 2% of the cases, respectively. The number of copula and modal verbs increased in five patients. The finiteness index decreased in five patients. MLU was higher than the normative data in only one patient.

Language-affecting variables

Stimulation conditions and parameters

Generally, the occurrence of deviating language samples varied among the stimulation conditions. Stimulation of only the right STN resulted in the least deviating language samples (70% of all language samples in that stimulation condition), while stimulation of the left STN only and bilateral stimulation off gave 75% and 86% deviating language samples, respectively. The largest number of deviating language samples were seen with bilateral stimulation on (93% of all language samples in that stimulation condition). However, there were high intra- and inter-subject variances between the different stimulation conditions over time and within the linguistic parameters.

In general, the average TEEDs remained symmetrical for the two electrode sides in all subjects at every test moment, but they progressively increased in the course of time. At an individual level, there were large inter-individual differences. The TEEDs are displayed in Table 8.2.

Table 8.2 Overview of the dopaminergic medication doses and total electrical energy delivered by deep brain stimulation.

		Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
LEDD (mg/day)								
Preoperatively		1420	842	817	780	810	1024	1311
1 month post-operatively		500	0	348	824	510	0	0
3 months post-operatively		640	310	464	510	305	240	0
6 months post-operatively		640	310	0	610	305	240	0
12 months post-operatively		740	390	0	610	305	240	0
TEED (Joule)								
1 month post-operatively	L	66,86	44,57	171,15	80,90	37,61	100,29	36,10
	R	66,86	25,07	160,62	37,61	16,71	100,29	88,42
3 months post-operatively	L	54,15	49,14	228,82	104,46	37,61	114,10	58,95
	R	80,90	32,20	267,43	66,86	16,71	100,29	88,42
6 months post-operatively	L	150,43	49,14	88,42	104,46	37,61	144,41	121,35
	R	204,75	32,20	140,57	60,34	13,54	144,41	104,46
12 months post-operatively	L	150,43	53,93	73,71	104,46	37,61	187,31	152,55
	R	204,75	36,10	241,35	60,34	13,54	187,31	104,46

Legend: LEDD= levodopa-equivalent daily dose expressed in milligrams a day; TEED = total electrical energy delivered for each electrode side; L= left electrode side; R = right electrode side.

Intelligibility

The intelligibility in 6 out of 7 patients (average intelligibility = 97%) stayed above 89%, with one patient never dropping below the dysarthria threshold of 96%. The intelligibility scores of one patient were clearly beneath those of all other subjects, with an average of 87% and a minimum of 70%.

Asymmetric dopamine depletion

Before surgery, none of the PD-left patients had deviating semantic parameters. Both PD-right patients had deviations in all semantic parameters except the number of nouns. After DBS surgery, all PD-left patients had deviating semantic parameters. The number of nouns was the most frequently (55%) deviating semantic parameter in PD-left patients, being reduced in all of them, followed by the number of lexical verbs (33%). For the two PD-right patients all semantic parameters deviated, although the number of nouns never showed deviations in the bilateral off condition.

Medication

In general, there was a distinct reduction in LEDD after STN surgery, although there were large inter-individual differences. One patient took no anti-Parkinson medication during the complete year after surgery. One patient had to augment anti-Parkinson medication the first month after surgery, while two months later the anti-Parkinson medication was reduced under the pre-operative level. Two other patients also needed continued anti-Parkinson medication but in a substantially lower dose than before surgery; it could be discontinued from the sixth month on in one patient and was systematically increased at every test moment in the other. Two patients took no anti-Parkinson medication the first month after surgery, but restarted in the third month. A last patient restarted anti-Parkinson medication from the sixth month after surgery. An overview of the LEDD can be found in Table 8.2.

Neuropsychological results

Prior to the STN surgery, the neuropsychological results of 5 out of 7 patients showed deficits. Two patients had slowed information processing. One patient had only moderate memory functions. The other two had a combination of deficits in executive functioning and information processing or memory functions. One year after STN surgery, there was a significant deterioration of memory functions in 4 out of 7 patients. Two of these patients' memory scores were still within the normal range; the others had moderate memory deficits. The information processing deteriorated significantly in 3 out of 7 patients. Executive functions deteriorated significantly in 6 out of 7 patients.

Prior to STN surgery, three patients reported mild depressive symptoms and four minimal depressive symptoms. There were no changes in the depressive symptoms one year after STN surgery for five patients. Two patients reported that their depressive symptoms were diminished a year after STN surgery. A schematic representation of the neuropsychological results is displayed in Table 8.3.

Discussion

The present study aimed to investigate the longitudinal evolution of spontaneous language in the first year after STN-DBS and to disclose variables that influence the effect of STN-DBS on linguistic outcome.

Most patients included in this study already exhibited linguistic problems prior to STN surgery. The deficiencies in spontaneous language production mainly consisted of morphosyntactical changes, which confirm previous research findings (Illes *et al.*, 1988) (Zanini *et al.*, 2009, Zanini *et al.*, 2010). The first month after surgery the accuracy of spontaneous language production noticeably decreased compared with the preoperative results, as highlighted by the significant decrease in the number of nouns. This decline in number of nouns persisted throughout the first post-operative year. Although based on the other deviating parameters, spontaneous language production seemed generally to improve from the third month on, which persisted in the sixth month, and retained at one-year post surgery.

These results are in contrast with the findings of Zanini *et al.* (2003), who found bilateral stimulation to generate a general improvement immediately 2 – 3 weeks after surgery. These opposite results are possibly due to methodological differences. In our study, a distinction was made within the word count between different word classes (e.g. lexical verbs, modular verbs, nouns…), which may have revealed deficits that were otherwise averaged out. Furthermore, Zanini et al. (2003) analysed spontaneous language production within a fixed number of minutes (5 minutes), compared to our study where the analysis was

Table 8.3 Schematic representation of het neuropsychological results divided into three subcategories and its evolution.

		Patient 1			**Patient 2**			**Patient 3**			**Patient 4**			**Patient 5**			**Patient 6**			**Patient 7**		
		Pre	Post	RCI	Pre	Post	RCI	Pre	Post	RCI	Pre	Post	RCI	Pre	Post	RCI	Pre	Post	RCI	Pre	Post	RCI
Memory	Encoding	+	+	○	▼	▼	○	+	+	○	+	+	✶	+	+	✶	+	▼	✶	▼	▼	✶
	Immediate recall	+	+	○	+	+	○	+	+	○	+	+	✶	+	+	○	+	▼	✶	+	▼	✶
	Delayed recall	+	+	○	+	+	○	+	+	○	+	+	○	+	+	○	+	+	○	+	▼	○
Information processing	Verbal working memory	+	+	○	+	+	○	+	+	○	+	+	○	+	+	○	+	+	○	+	+	○
	Processing speed	▼	NA	NA	+	▼	✶	▼	▼	○	+	+	○	+	+	○	▼	▼	✶	+	▼	✶
Executive functioning	Phonological word fluency	+	NA	NA	+	+	○	+	+	✶	+	+	○	+	+	○	+	+	○	+	+	✶
	Semantic word fluency	▼	+	○	+	+	✶	+	+	✶	+	+	✶	+	+	○	+	+	○	+	+	○
	Interference	+	NA	NA	▼	▼	✶	+	+	○	+	+	✶	+	+	✶	+	▼	✶	+	+	✶

Legend: pre= preoperative testing; post = postoperative testing; RCI= reliable change index; NA = not available; + = score within the normal range; ▼= score significant lower than normative range; ✶= reliable decline compared to preoperative neuropsychological measures, ○ = no change over time on neuropsychological measures.

done on a fixed number of words (300 words), which can make a substantial difference in the word count. Another difference was the medication intake: all patients included in the study of Zanini *et al.* (2003) were evaluated after STN surgery without anti-Parkinson medication, while in the present study all patients maintained their optimal, yet clearly reduced, doses of anti-Parkinson medication during testing. The relationship between dopaminergic medication and high-level cognitive functions, such as spontaneous language, is highly complex. The effect of dopaminergic medication often seems paradoxical, leading to both improvements and impairments, as excessive as well as insufficient levels of dopamine seem to impair performance (Cools and D'Esposito, 2011). The levels of dopamine depletion in the dorsal striatum in patients with Parkinson´s disease seem to differ from those in ventral parts of the striatum and the mesocorticolimbic dopaminergic system. Hence, the doses of dopaminergic medication required rectifying the dopamine deficits in the dorsal striatum may lead to overdosing of the broad ventral striato-frontal circuitry (Cools, 2006). STN-surgery leads to a substantial decrease in the need of dopaminergic medication. It has been suggested that this drastic reduction might cause impairments (Yamanaka *et al.*, 2012). Others have hypothesized that deterioration after STN-DBS does not depend on the degree of medication reduction, but instead on the amount of dopaminergic medication taken preoperatively (Heo *et al.*, 2008). Because patients in this study took their dopaminergic medication during testing, the alterations in dopaminergic medication might have influenced the study outcome. Unfortunately, the lack of detailed information on the dopaminergic medication in the study of Zanini *et al.* (2003) precludes further comparisons with our study. Another possible explanation for the difference in results compared to the study of Zanini *et al.* (2003) is the interaction of medication with DBS stimulation. Dopaminergic medication and STN-DBS both seem to influence the functioning of the prefrontal cortex, but in a different way. While dopaminergic medication saturates the frontal cortex with dopamine, STN-DBS seems to reduce activation in the left inferior frontal cortex (Schroeder *et al.*, 2003). The combination of both therapies might be more beneficial than each therapy separately, provided that the dopaminergic medication is correctly dosed so that it can partly neutralize the stimulation-induced inactivation of the prefrontal cortex (Mondillon *et al.*, 2012).

The prominent reduction in number of nouns for patients with STN-DBS has been described before (Batens, 2014; Batens, 2015). Nouns obtain a thematic role in a grammatical structure and can be partially replaced by function words (e.g. pronouns). Verbs on the contrary have a dominant role in sentence generation, as an assigner of thematic roles (Altmann & Troche, 2011). Therefore, the vast majority of sentences in spontaneous language production have to include a verb. It has been suggested that in order to be able to assign thematic roles, patterns of activity within a recurrent prefrontal network are necessary (Bates, McNew, Macwhinney, Devescovi, & Smith, 1982; Dominey & Inui, 2009). The resulting patterns need encoding by the striatum to map open class elements, such as nouns, onto their appropriate thematic roles (Hinaut & Dominey, 2013). Especially the left prefrontal areas with their subcortical connections are involved in these syntactic processes (Dominey & Inui, 2009). Recently, neuro-anatomical evidence for this syntactic network has been provided, indicating that a cortico-basal ganglia-thalamocortical circuit, including Broca's area and the caudate nucleus, is involved in complex syntactic processes (Teichmann et al., 2015).

The possible influence of dopaminergic medication can also be inferred from the significant decrease in number of produced nouns after DBS surgery and the concomitant reduction of medication. None of the patients had a decreased number of nouns preoperatively, while after surgery this became the second largest deviating parameter that persisted one-year post surgery. Asymmetric dopamine depletion appears to play an important role. PD-left patients showed a marked decrease in the number of nouns in the condition without DBS stimulation, whereas for the two PD-right patients no significant decrease in the number of nouns was detectable when STN stimulation was turned off. This decline suggests that the dopamine depletion in the left hemisphere causes a deterioration that cannot be neutralized by the combination of STN with the reduced amount of dopaminergic medication. Although PD-right patients did not exhibit a reduced amount of nouns without STN-stimulation, combining both therapeutic options apparently reduced the number of nouns for PD-right, indicating that STN-DBS might lower the activation of the left frontal structures.

The impact of surgical microlesioning in the initial phase after STN surgery has never been investigated with respect to spontaneous language production, but cannot be excluded (Pourfar *et al.*, 2009, Jech *et al.*, 2012). The insertion of electrodes themselves have been reported to yield both clinical improvement (e.g. motor symptoms (Granziera *et al.*, 2008)) and deterioration (e.g. verbal fluency (Lefaucheur *et al.*, 2012)), although the clinical symptoms of microlesioning should disappear within the first month after implantation (Jech *et al.*, 2012). If microlesioning would cause an initial deterioration of language processing, one would have expected the same deterioration in the study of Zanini *et al.* (2003), specifically because their first evaluation was even earlier after surgery. Finally, due to the absence of a control Parkinson's disease group without STN-DBS and by maintaining the medication state during testing, no hypothesis could be made with respect to disease progression. The improvement of spontaneous language production within the course of the first year, however, suggests that the linguistic changes cannot be solely attributed to disease progression.

The highly inter-individual variability in Parkinson's disease, and in particular to DBS-STN, has been reported several times with respect to non-motor symptoms and was confirmed in the present study (Fasano *et al.*, 2012, Klostermann *et al.*, 2012). In this longitudinal study, three patients stood out from the others. The first one (patient 5) was distinct from the group because of the high number of new deviating parameters after surgery. The other two patients (patient 1 and patient 4) on the other hand, had remarkably less deviating language samples in comparison with the group. The opposite linguistic results of these three patients after STN surgery offer the opportunity to compare different variables that possibly interact with spontaneous language production. To date it is still a matter of debate whether the subcortical network serves a language specific function or rather general cognitive control functions (Chan *et al.*, 2013; Colman *et al.*, 2009). In the present study, the patient with the most additional language production deficits scored within the normal range both before and one year after STN surgery on all neuropsychological tests, although both memory and executive functions decreased significantly compared with the pre-operative results. The same neuropsychological observation applied for one of the patients with the best spontaneous language production after STN-surgery. Despite their comparable neuropsychological profile, their outcome on language production differs, which argues against neuropsychological functioning being the key factor in these patients' language production outcome. Depressive symptoms did not seem to be the cause of the individual language differences either, as none of the patients exhibited more depressive symptoms one year after STN-surgery. This reasoning, however, does not take into account possible mood fluctuations during the year, because of the absence of measurements. Another suggestion that has been made is that linguistic problems in patients with Parkinson´s disease originate from attempts to circumvent speech difficulties (Illes *et al.*, 1988, Illes, 1989). One would expect that the patients with the highest speech intelligibility scores would have the lowest linguistic deviations. However, based on the speech intelligibility scores, this hypothesis is not confirmed for the present patient group.

What did stand out in the two patients with the best spontaneous language production compared to the others was the dosage of anti-Parkinson medication after surgery. These patients received the highest amount of dopaminergic medication after STN-DBS of all included patients, in combination with an average STN-DBS intensity. The patient with the highest number of new deviating parameters had the lowest TEED in combination with an above average amount of anti-Parkinson medication. As already proposed before, a beneficial spontaneous language outcome seems to require that STN-DBS be combined with a sufficient amount of dopaminergic medication (Mondillon *et al.*, 2012).

Conclusion

STN-DBS seems to influence the already compromised spontaneous language production negatively, which is mainly due to a significant decrease in number of nouns after STN-DBS. The decrease in number of nouns can be explained by their thematic role in sentences, indicating that the introduction of STN-DBS might cause disturbances of the cortico-basal ganglia-thalamocortical network involved in complex syntactic processes. The interaction of dopaminergic medication and STN-stimulation seems to play a role in the language outcome and provides an explanation for the highly individual results of spontaneous language production after STN-DBS.

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General discussion

PART 3

The current literature on spontaneous language production in PD is rather limited, providing fragmented elements of information. The same accounts for the effect of STN-DBS on spontaneous language production, with only one study so far that examines spontaneous language production at multiple moments in the course of time. The intent of this doctoral thesis was to provide a more detailed description on the semantic and morphosyntactic features of spontaneous language production in PD with STN-DBS and this consecutively within the first year after surgery. STN-DBS offers the opportunity to evaluate unilateral stimulation effects, which is especially interesting in view of the asymmetric hemispherical representation of both language functions and PD. Finally, because spontaneous language production is being used to participate in daily life, an exploratory trial was set up to evaluate the interaction between pragmatic production skills and STN-DBS, as presently no data are available on this subject.

Linguistic characteristics of spontaneous language production in PD

The spontaneous language production of PD patients clearly diverged from healthy subjects; especially the morphosyntactic features seemed impaired. PD patients produced shorter, more incorrect sentences, which confirms previous research findings (Illes, 1989; Illes, Metter, Hanson, & Iritani, 1988; Murray, 2000; Murray & Lenz, 2001; Zanini, Tavano, & Fabbro, 2010). A recurrent result in previous studies (at word- and sentence level) was the distinctly larger impairment of verbs compared to nouns (e.g. (Boulenger et al., 2008; Cotelli et al., 2007; Peran et al., 2003). The involvement of frontal cortical motor areas, selection and inhibition deficits, and general executive dysfunctions, have been put forward as possible explanations for this discrepancy (Boulenger et al., 2008; Cotelli et al., 2007; Crescentini, Mondolo, Biasutti, & Shallice, 2008). However, in our studies, a recurring change in spontaneous language production was the reduced number of nouns, instead of verbs. Remarkably, none of the PD patients had a decreased production of nouns prior to surgery, while this became one of the largest deviating parameters after surgery, persisting throughout the year. Asymmetric dopamine depletion appeared to be influential, as only PD-left patients produced less nouns compared to the normative data in both the prospective studies as the longitudinal study, while both PD-right patients in the longitudinal study showed no declined number of nouns when STN stimulation was turned off.

Usually the number of nouns is being contemplated as a semantic parameter, but nouns may also be viewed from their grammatical function (Grossman et al., 2003; Peran et al., 2003). Nouns obtain a thematic role in a grammatical structure and can be partially replaced by function words (e.g. pronouns). Verbs on the contrary have a dominant role in sentence generation, as an assigner of thematic roles (Altmann & Troche, 2011). Therefore, the vast majority of sentences in spontaneous language production have to include a verb. It has been suggested that in order to be able to assign thematic roles, patterns of activity within a recurrent prefrontal network are necessary (Bates, McNew, Macwhinney, Devescovi, & Smith, 1982; Dominey & Inui, 2009). The resulting patterns need encoding by the striatum to map open class elements, such as nouns, onto their appropriate thematic roles (Hinaut & Dominey, 2013). Especially the left prefrontal areas with their subcortical connections are involved in these syntactic processes (Dominey & Inui, 2009). Reduced noun production can therefore be the result of morphosyntactic difficulties due to dysfunctional left hemispheric cortico-basal ganglia-thalamocortical networks. The lateralisation of syntactic processes might be accountable for the discrepancy between PD-left and PD-right patients.

The only study that examined the number of nouns in spontaneous language production did not find any differences between PD patients and healthy controls (Pignatti, Ceriani, Bertella, Mori, & Semenza, 2006). The patients included in the study of Pignatti et al. (2006) did not have STN-DBS, which is in line with the finding of our longitudinal study where PD patients showed no decline in number of nouns before surgery. STN-surgery leads to a substantial reduction of dopaminergic medication, which has been suggested to cause impairments (Yamanaka et al., 2012). Others have hypothesized that deterioration after STN-DBS did not depend on the degree of medication reduction, but on the amount of dopaminergic medication taken preoperatively (Heo et al., 2008). The relationship between dopaminergic medication and high-level cognitive functions, such as spontaneous language, is highly complex. The effect of dopaminergic medication often seems paradoxical, leading to both improvements and impairments, because excessive as well as insufficient levels of dopamine seem to impair performances (Cools

& D'Esposito, 2011). The levels of dopamine depletion in the putamen and dorsal striatum in PD patients seem to differ from those in the ventral parts of the striatum and the mesocorticolimbic dopaminergic system. Hence, the doses of dopaminergic medication needed to rectify the dopamine deficits in the putamen and dorsal striatum may lead to overdosing the broad ventral striato-frontal circuitry (Cools, 2006). However, changes in medication doses cannot fully explain the decrease in number of nouns, because prior to surgery without their medication PD-patients did not exhibit a reduction in number of nouns. Perhaps the placement of the STN electrodes has induced the reduction of noun production. Although the presence of electrodes and the impact of surgical microlesioning in the initial phase after STN surgery has never been investigated with respect to language production, it cannot be excluded (Jech et al., 2012; Pourfar et al., 2009). The insertion of electrodes themselves has been reported to contribute to clinical improvement (motor symptoms (Granziera et al., 2008)) as well as worsening (e.g. verbal fluency (Lefaucheur et al., 2012)), although the clinical symptoms of microlesioning should disappear within the first month after implantation (Jech et al., 2012), while in our study the declined number of nouns persisted throughout the year. The discrepancy between PD patients with and without STN-DBS, even when STN stimulation has been turned off, indicates that the results found in one of these PD groups cannot be blindly transposed to the other group.

The presence of morphosyntactic difficulties was also confirmed by a diminished finiteness index and an enlarged use of copula and modals verbs. Again asymmetric dopamine depletion seemed to influence both parameters, but in a contradictory way. Although morphosyntactic processes are assigned to the left cortico-basal ganglia-thalamocortical circuits, it were PD-right patients that had a significant lower finiteness index than PD-left patients, while only PD left patients showed an excessive use of copula and modals verbs. One could argue that the low finiteness index originates from left hemispheric syntactic language deficits. First, there was a significant decrease of the finiteness index in both PD groups, indicating that both groups encounter difficulties with verb inflection compared to healthy subjects. Second, by replacing lexical verbs by high frequent, irregular, non-lexical verbs, PD patients avoid inflection of lexical verbs. On the other hand, by incorporating copular and modal verbs into a sentence, the mapping of open class words can be postponed to the rear end of the grammatical structure (Bastiaanse, 2011; Hinaut & Dominey, 2013). Either way, the overuse of copula and modal verbs can be a compensatory mechanism or to avoid inflection of lexical verbs or to facilitate grammatical role assignment. As morphosyntax is assigned to the left hemispheric processes, perhaps PD left patients experience verb inflection problems earlier in the course of the disease, enabling them to develop compensatory strategies. In contrast to PD-right patient, who might start to experience verb inflection problems when the depletion of the nigrostriatal system became bilateral, hence at a moment at which compensatory possibilities were already limited. Unfortunately, because of the lack of functional imaging data in our studies, all assumptions on neural reorganization remain speculative.

Effects of STN-DBS on spontaneous language production in PD

The results of the included studies indicated that the effect of STN-DBS on spontaneous language production was not straightforward and that a multitude of variables influenced the outcome. These findings are in line with previous research where STN-DBS resulted in divergent results. Asymmetric dopamine depletion was one of the variables that influenced the effect of STN-DBS on the linguistic and pragmatic outcome. When asymmetric depletion of the nigrostriatal network was taken into account, stimulation effects on linguistic parameters were present for PD-left patients. This is in contrast to the PD-right patients, where no linguistic deviations between the different stimulation conditions were detectable. The PD-left group seemed to benefit from STN stimulation, producing a larger number of nouns and longer sentences with bilateral stimulation on, compared to bilateral stimulation off. Stimulation of only the right STN in PD-left patients normalized the number of copula modal verbs compared to stimulation of only the left STN. For all subjects, the left hemisphere was assigned to be the language-dominant one. It has been suggested that STN stimulation has a negative effect on the hemisphere specific language functions (Holtgraves, McNamara, Cappaert, & Durso, 2010; Schulz et al., 2012). Because the most observed deviations could be classified as morphosyntactic deficit and morphosyntactic processes that are allocated to the left hemisphere (Dominey & Inui, 2009; Lindell, 2006; Menenti, Segaert, &

Hagoort, 2012), one would expect a decline by stimulation of the left STN only, which was not the case. However, when the linguistic data of each stimulation condition were compared with the normative data, it was the stimulation of only the right STN in each study that approached closest normative data. So perhaps for PD-left patients, stimulation of the least dysfunctional nigrostriatal network is necessary to normalize spontaneous language production, in contrast with the idea that STN stimulation has a negative effect on hemisphere-specific language functions (Schulz et al., 2012). Interesting, for pragmatic production skills, PD-right patients had a tendency to explain more during a conversation when only the left STN was stimulated, compared to the other stimulation conditions. The ability to give an explanation is inherently linked to right hemispheric linguistic and cognitive functions (Mitchell, & Crow, 2005; Perkins, 2012). Again, this suggests that stimulation of the least dysfunctional nigrostriatal increases the ability to explain something. However, as pragmatic production demands a bilateral cortical involvement, one would expect that STN-stimulation also altered the pragmatic production for PD-left patients, but this discrepancy could not be found. Nevertheless, it ratifies the idea that DBS stimulation is task-specific and the outflow pathways are affected differently depending on the task (Schulz et al., 2012; Thobois & Broussolle, 2012; Thobois et al., 2007).

While asymmetric dopamine depletion is obviously one of the influencing variables, it became clear that it could not explain all the effects of STN-DBS on spontaneous language production. Especially in the longitudinal evaluation, the high inter- and intra-individual differences were striking. While a number of variables were included in the longitudinal study (asymmetric dopamine depletion, lateralization of stimulation, stimulation parameters, medication dosage, speech intelligibility, mood, and neuropsychological performances), it was difficult to determine clearly the interaction between these variables and STN-DBS effects. The interaction of dopaminergic medication with STN-DBS was the only other variable, besides asymmetric dopamine depletion, that stood out in the longitudinal study. While in both prospective studies the linguistic outcome seemed to improve partially with bilateral stimulation on, the results of the longitudinal study indicated that this was very individually determined. Therefore, group means did not seem to capture the individual effects of STN-DBS on spontaneous language while on a clinical basis these individual results are particularly important (Yágüez et al., 2014).

Functional anatomical considerations

All assumptions on functional (re)organisation of the cortico-basal ganglia-thalamocortical-circuits based on the results of this thesis are speculative due to the lack of functional imaging data. However, our results do indirectly confirm some hypothesis put forward in other studies. Our data seem to confirm that the lateralisation of subcortical language functions mimics the cortical language predominance.

The computer model for syntactic processing investigated by Dominey, et al. (2009) and recently confirmed in a clinical study by Teichmann, et al. (2015), proposed the connection between the Broca's area and the basal ganglia (head of caudate according to Teichmann et al., 2015). Our clinical data are in line with these findings, as our patients clearly experience morphosyntactic difficulties, especially with the mapping of nouns into syntactical structures.

Future perspective

Because spontaneous language production in relationship to PD and STN-DBS is still in its explorative phase, the research opportunities are ample. Therefore, only a few research opportunities are highlighted here, which might lead to substantial progression.

Based on our studies, it can be concluded that PD patients experience linguistic changes in the course of the disease, where multiple variables need to be kept in mind. Due to the chronic progression of the disease, the brain will try to compensate the dopamine depletion (Appel-Cresswell, de la Fuente-Fernandez, Galley, & McKeown, 2010) and the associated linguistic deficits. However, knowledge of the progression of linguistic deficits and the neurophysiological adaptation of the brain in response to the progression of the disease is still an unexplored domain. A long-term follow-up of PD patients from the moment of diagnose until the advanced stage of the disease would shed a light on these linguistic changes. The integration of functional neuroimaging data would be essential to clarify the neural compensatory mechanisms present at the different stages of the disease. The identification of the neural reorganisation would also clarify the possible differences in reorganisation between subgroups of PD patients. Ideally, this type of research would be conducted with PD patients on and off their anti-Parkinson medication, in order to elucidate the interaction with dopaminergic medication further.

Another intriguing question that remains is if the contribution of the BG in language processes is domain specific or not. The introduction of a cognitive test that distinguishes between linguistic and non-linguistic (Chan, et al., 2013) into language research, might further disentangle the interaction between cognition and language in BG processes.

In terms of the effect of STN-DBS on spontaneous language production, the outcome seems to be influenced by a high amount of influencing variables. One recurrent aspect that might have a great impact but has never been investigated in terms of language processes are the stimulation settings. Yet, all studies investigated the effect of STN-DBS on language with stimulation settings tuned to give patients an optimal clinical benefit. It would be interesting to investigate which stimulation setting would be linguistically most beneficial and compare these results with comparable studies investigating optimal stimulation setting for speech and cognition. This information could be a great added value for the programming of the current types of DBS device and can challenge the manufacturers of DBS devices in the development of devices which can transmit multiple stimulation settings.

Finally, although the analysis of spontaneous language production offers a wealth of information, the great challenge currently is to translate this information into treatment strategies. Despite the recognition of language deficits in PD patients, no research has been done so far to improve those deficits.

Clinical considerations.

Our results suggest that the spontaneous language production of PD patients with STN-DBS is altered and differs from PD patients without STN-DBS. An individual approach in clinical practice is necessary to obtain the optimal linguistic outcome, where at least asymmetric dopamine depletion, medication dosage, and stimulation parameters have to be taking into account. In order to accomplish the optimal clinical outcome, an interdisciplinary collaboration is necessary.

At this point, no standardized linguistic tests are available to detect specifically the linguistic problems associated with PD, although these linguistic changes cannot be ignored. Clinicians should be attentive for linguistic alterations and inquire their PD patients whether they have experienced linguistic changes. Furthermore, based on the results of this doctoral thesis it is advisable to map the spontaneous language production of PD patients pre- and postoperatively with the ASTA (Boxum, van der Scheer, & Zwaga, 2010). The ASTA should be conducted preoperatively, with and without their anti-Parkinson medication, and postoperatively in the four stimulation conditions. As the execution of the ASTA is very time-consuming, it would be interesting to develop a quick screenings instrument specifically for PD patients that could provide morphosyntactic and semantic information that has an excellent correlation with their spontaneous language production. This would enable the clinician to examine patients under a variety of pharmacological and stimulation conditions, providing individual information of the effect of influencing variables. As for therapeutic possibilities, currently no recommendation can be provided.

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